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Catalytic asymmetric conjugate addition of Grignard reagents to chromones

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General Methods:

Column chromatography was performed on silica gel (Silica-P flash silica gel from Silicycle, size 40-63 μm). TLC was performed on silica gel 60/Kieselguhr F254. Components were visualized by UV and staining with a solution of a mixture of $KMnO_4$ (10 g) and K_2CO_3 (10 g) in H_2O (500 mL). Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). ^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 101 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: d 7.26 for ^{1}H, d 77.0 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, p =pentet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured in $CHCl_3$ on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Conversion of the reaction was determined by GC (GC, HP6890: MS HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA). Enantiomeric excess values were determined by HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector. All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. All solvents were reagent grade and were dried and distilled prior to use, if necessary. Tetrahydrofuran (THF), tert-butyl methyl ether (*t*-BuOMe) and diethylether (Et_2O) were distilled over Na/benzophenone. Toluene and dichloromethane (CH_2Cl_2) were distilled over calcium hydride. All the ligands, copper salts and chromanones were purchased from Aldrich, ABCR and Acros and used as received. Grignard reagents RMgBr (R = Et, *n*-pentyl, *n*-hexyl, *i*-Bu, 3-pentyl, dodecyl, cyclopentyl) were purchased from Aldrich. Phenethylmagnesium bromide and but-3-en-1-ylmagnesium bromide were prepared from the corresponding alkyl bromides and magnesium turnings in Et_2O following standard procedures. Grignard reagents were titrated using *sec*-BuOH and catalytic amounts of 1,10-phenanthroline.

General procedure for the synthesis of the racemic product of the copper catalyzed 1,4-addition addition of Grignard reagents to chromones

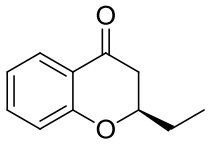
$CuBr{\cdot}SMe_2$ (0.01 mmol, 2.02 mg) and PPh_3 (0.012 mmol, 6.3 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) were added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone (0.2 mmol) in DCM (1.0 mL) was added dropwise. The reaction mixture was stirred until TLC (*n*-pentane:EtOAc 9:1) showed full conversion and quenched with saturated aqueous NH_4Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under *vacuo*. Purification by flash chromatography over silica gel, using *n*-pentane:Et_2O 9:1 afforded the desired compounds. (The reaction in some cases shown 1,2 and 1,4 addition products)

General procedure for the asymmetric 1,4-addition of Grignard reagents to chromones:

$CuBr{\cdot}SMe_2$ (0.01 mmol, 2.02 mg) and **L4** (*R,S*)-Rev-Josiphos (0.012 mmol, 7.2 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) was added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone (0.4 mmol) in DCM (1.0 mL) was added slowly over 1h using a syringe pump. The reaction was stirred until TLC (*n*-pentane:EtOAc 9:1) showed full conversion and quenched with saturated aqueous NH_4Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under *vacuo*. Purification by flash chromatography over silica gel, using *n*-pentane:Et_2O 9:1 afforded the desired compounds.

Characterization of products 2, 3, 4, 5, 6, 7

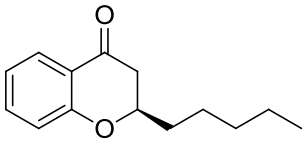
(*R*)-2-ethylchroman-4-one (2a)[1]



Synthesized according the general procedure, obtained in 98% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 14.2 min, minor enantiomer t_r = 16.0 min, ee= 95%; $[\alpha]^{25}_D$= +51.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 7.8, 1.3 Hz, 1H), 7.44 (td, J = 7.8, 1.6 Hz, 1H), 7.03-6.88 (m, 2H), 4.45-4.29 (m, 1H), 2.66 (d, J = 7.8 Hz, 2H), 1.88 (dp, J = 14.7, 7.4 Hz,

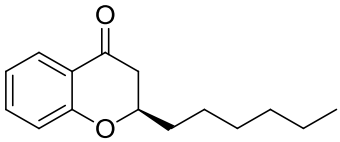
1H), 1.81-1.69 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 161.6, 135.8, 126.8, 121.0, 120.9, 117.8, 78.9, 42.4, 27.9, 9.2 ppm; HRMS (ESI) calculated for $C_{11}H_{13}O_2$ [M + H] 177.0910 found 177.0910.

(R)-2-pentylchroman-4-one (2b)



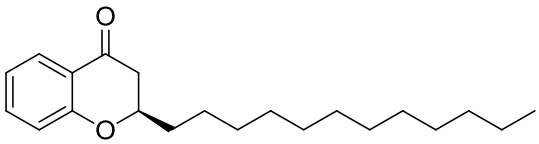
Synthesized according the general procedure, obtained in 80% yield; oil;enantiomeric excess was determined by HPLC (Chiracel OBH), hexane:i-PrOH 99:1, 0.5 mL/min, minor enantiomer t_r = 12.3 min, major enantiomer t_r = 12.9 min, ee= 96%; $[\alpha]^{25}_D$= +48.9 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.46 (td, J = 8.0, 1.6 Hz, 1H), 7.02-6.94 (m, 2H), 4.43 (qd, J = 7.6, 5.2 Hz, 1H), 2.68 (d, J = 7.5 Hz, 2H), 1.88 (dddd, J = 12.8, 10.1, 7.4, 5.3 Hz, 1H), 1.75-1.64 (m, 1H), 1.61-1.41 (m, 2H), 1.39-1.29 (m, 4H), 0.91(t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 161.7, 135.9, 126.9, 121.1, 121.0, 117.8, 77.9, 43.0, 34.9, 31.5, 24.5, 22.5, 14.0 ppm; HRMS (ESI) calculated for $C_{14}H_{19}O_2$ [M + H] 219.1380 found 219.1379.

(R)-2-hexylchroman-4-one (2c)



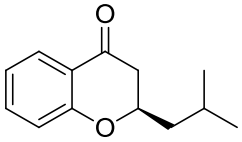
Synthesized according the general procedure, obtained in 87% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 12.1 min, minor enantiomer t_r = 12.8 min, ee= 96%; $[\alpha]^{25}_D$= +51.3 (c 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.8, 1.6 Hz, 1H), 7.44 (td, J = 7.8, 1.5 Hz, 1H), 7.00-6.94 (m, 2H), 4.42 (qd, J = 7.6, 5.4 Hz, 1H), 2.67 (d, J = 7.9 Hz, 2H), 1.93-1.81 (m, 1H), 1.69 (ddd, J = 13.9, 10.4, 5.4 Hz, 1H), 1.60-1.40 (m, 2H), 1.39-1.21 (m, 6H), 0.89 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 161.7, 135.9, 126.9, 121.1, 121.0, 117.9, 77.9, 43.0, 34.9, 29.0, 24.8, 22.6, 14.0 ppm; HRMS (ESI) calculated for $C_{15}H_{21}O_2$ [M + H] 233.1536 found 233.1537.

(R)-2-dodecylchroman-4-one (2d)



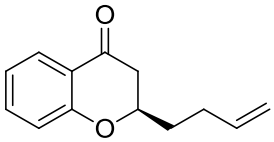
Synthesized according the general procedure, obtained in 53% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 11.5 min, ee= 86%; $[\alpha]^{25}_D$= +24.5 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, J = 7.8, 1.6 Hz, 1H), 7.41 (td, J = 7.8, 2.0 Hz, 1H), 6.96-6.91 (m, 2H), 4.41-4.35 (m, 1H), 2.63 (d, J = 7.9 Hz, 2H), 1.89-1.77 (m, 1H), 1.71-1.60 (m, 1H),1.55-1.35 (m, 2H), 1.33-1.10 (m, 18H), 0.83 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 161.6, 135.8, 126.9, 121.0, 120.9, 117.8, 77.9, 42.9, 34.9, 31.9, 29.63, 29.59, 29.57, 29.49, 29.43, 29.32, 29.29, 24.8, 22.6, 14.0 ppm; HRMS (ESI) calculated for $C_{21}H_{33}O_2$ [M + H] 317.2475 found 317.2477.

(R)-2-isobutylchroman-4-one (2e)



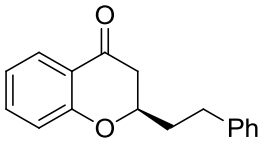
Synthesized according the general procedure, obtained in 82% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 12.4 min, minor enantiomer t_r = 13.2 min, ee= 98%; $[\alpha]^{25}_D$= +57.2 (c 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J = 7.8, 1.5 Hz, 1H), 7.34 (td, J = 7.8, 1.6 Hz, 1H), 6.90-6.83 (m, 2H), 4.45-4.36 (m, 1H), 2.61-2.48 (m, 2H), 1.88-1.71 (m, 2H), 1.34 (ddd, J = 13.8, 7.9, 4.6 Hz, 1H), 0.864 (d, J = 6.4 Hz, 3H), 0.857 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 161.6, 135.9, 126.9, 121.1, 121.0, 117.9, 76.3, 43.9, 43.4, 24.2, 23.0, 22.2 ppm; HRMS (ESI) calculated for $C_{13}H_{17}O_2$ [M + H] 205.1223 found 205.1223.

(R)-2-(but-3-en-1-yl)chroman-4-one (2f)



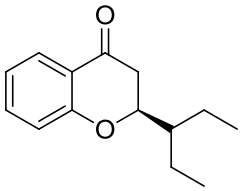
Synthesized according the general procedure, obtained in 79% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 15.3 min, minor enantiomer t_r = 17.1 min, ee= 87%; $[\alpha]^{25}_D$= +44.4 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.3 Hz, 1H), 7.41 (t, J = 7.3 Hz, 1H), 6.98-6.90 (m, 2H), 5.79 (ddt, J = 16.9, 10.1, 6.6 Hz, 1H), 5.03 (d, J = 17.1 Hz, 1H), 4.97 (d, J = 10.2 Hz, 1H), 4.45-4.37 (m, 1H), 2.64 (d, J = 7.7 Hz, 2H), 2.33-2.16 (m, 2H), 1.95 (td, J = 14.2, 8.0 Hz, 1H), 1.74 (ddd, J = 13.9, 8.9, 6.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 161.5, 137.2, 135.9, 126.9, 121.2, 121.0, 117.8, 117.5, 77.0, 42.9, 34.0, 29.0 ppm; HRMS (ESI) calculated for $C_{13}H_{15}O_2$ [M + H] 203.1067 found 203.1066.

(*R*)-2-phenethylchroman-4-one (2g)[2]



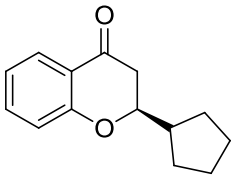
Synthesized according the general procedure, obtained in 77% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 95:5, 0.5 mL/min, major enantiomer t_r = 29.2 min, minor enantiomer t_r = 12.5 min, ee= 75%; $[\alpha]^{25}_D$= +56.7 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, J = 8.1, 1.7 Hz, 1H), 7.49 (td, J = 7.8, 1.6 Hz, 1H), 7.32-7.29 (m, 2H), 7.26-7.19 (m, 3H), 7.03-7.00 (m, 2H), 4.44 (ddt, J = 11.0, 8.6, 4.5 Hz, 1H), 2.96-2.81 (m, 2H), 2.77-2.65 (m, 2H), 2.23 (dtd, J = 14.2, 8.6, 5.7 Hz, 1H), 2.00 (dddd, J = 13.9, 9.2, 7.2, 4.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 161.5, 140.9, 136.0, 128.5, 128.4, 127.0, 126.2, 121.3, 121.1, 117.9, 76.8, 43.0, 36.5, 31.1 ppm; HRMS (ESI) calculated for $C_{17}H_{17}O_2$ [M + H] 253.1223 found 253.1224.

(*S*)-2-(pentan-3-yl)chroman-4-one (2h)



Synthesized according the general procedure, obtained in 68% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 11.4 min, minor enantiomer t_r = 12.3 min, ee= 84%; $[\alpha]^{25}_D$= + 53.5 (c 0.92, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (ddd, J = 8.4, 7.3, 1.8 Hz, 1H), 7.01-6.94 (m, 2H), 4.43 (ddd, J = 13.5, 4.9, 2.70 Hz, 1H), 2.75 (dd, J = 16.6, 13.5 Hz, 1H), 2.60 (dd, J = 16.6, 2.7 Hz, 1H), 1.69-1.59 (m, 2H), 1.58-1.49 (m, 2H), 1.36 (dt, J = 15.7, 7.9 Hz, 1H), 0.96 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 162.1, 135.8, 126.9, 121.0, 117.9, 79.5, 44.8, 40.0, 21.5, 21.3, 11.4 ppm; HRMS (ESI) calculated for $C_{14}H_{19}O_2$ [M + H] 219.1380 found 219.1380.

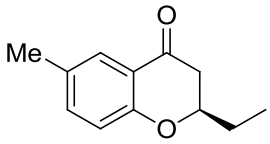
(*S*)-2-cyclopentylchroman-4-one (2i)



Synthesized according the general procedure, obtained in 79% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 13.8 min, minor enantiomer t_r = 14.5 min, ee= 97%; $[\alpha]^{25}_D$= +72.1 (c 0.9,

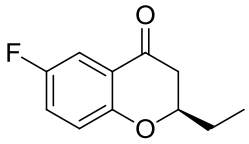
$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, J = 7.8, 1.3 Hz, 1H), 7.45 (td, J = 7.8, 1.7 Hz, 1H), 7.00-6.93 (m, 2H), 4.22 (ddd, J = 9.6, 7.8, 5.7 Hz, 1H), 2.74-2.64 (m, 2H), 2.28-2.20 (m, 1H), 1.97-1.89 (m, 1H), 1.79-1.74 (m, 1H), 1.72-1.50 (m, 5H), 1.37-1.25 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 161.8, 135.9, 126.9, 121.04, 121.0, 117.9, 81.7, 44.1, 42.2, 28.8, 28.4, 25.5, 25.4 ppm; HRMS (ESI) calculated for $C_{14}H_{17}O_2$ [M + H] 217.1223 found 217.1223.

(*R*)-2-ethyl-6-methylchroman-4-one (3)



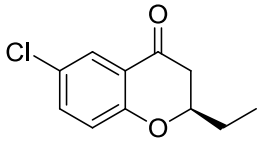
Synthesized according the general procedure, obtained in 93% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 13.8 min, minor enantiomer t_r = 15.2 min, ee= 92%; $[\alpha]^{25}_D$= +69.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 1.3 Hz, 1H), 7.25 (dd, J = 8.4, 2.1 Hz, 1H), 6.86 (d, J = 8.4, 1H), 4.32 (qd, J = 7.6, 5.6 Hz, 1H), 2.64 (d, J = 8.0 Hz, 2H), 2.28 (s, 3H), 1.87 (dp, J = 14.4, 7.3 Hz, 1H), 1.80-1.68 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 159.7, 137.0, 130.5, 126.4, 120.6, 117.6, 79.0, 42.6, 28.0, 20.4, 9.3 ppm; HRMS (ESI) calculated for $C_{12}H_{15}O_2$ [M + H] 191.1067 found 191.1065.

(*R*)-2-ethyl-6-fluorochroman-4-one (4)



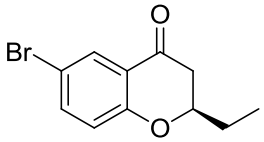
Synthesized according the general procedure, obtained in 75% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 12.9 min, minor enantiomer t_r = 14.3 min, ee= 92%; $[\alpha]^{25}_D$= +72.3 (c 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, J = 8.3, 3.1 Hz, 1H), 7.12 (td, J = 8.6, 3.2 Hz, 1H), 6.89 (dd, J = 9.0, 4.2, 1H), 4.29 (m, 1H), 2.66-2.62 (m, 2H), 1.83 (dp, J = 14.7, 7.4 Hz, 1H), 1.77-1.65 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.9 (td, $J_{H\text{-}F}$ = 8.0, 4.3) ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8 (d, $J_{C\text{-}F}$ = 1.8), 158.0 (d, $J_{C\text{-}F}$ = 31.6), 156.9 (d, $J_{C\text{-}F}$ = 208.6), 123.4 (d, $J_{C\text{-}F}$ = 24.6), 121.4 (d, $J_{C\text{-}F}$ = 6.5), 119.5 (d, $J_{C\text{-}F}$ = 7.3), 111.8 (d, $J_{C\text{-}F}$ = 23.2), 79.3, 42.2, 27.8, 9.2 ppm; HRMS (ESI) calculated for $C_{11}H_{12}FO_2$ [M + H] 195.0816 found 195.0815.

(*R*)-6-chloro-2-ethylchroman-4-one (5)



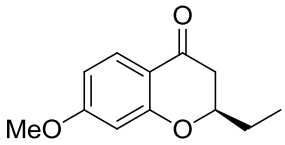
Synthesized according the general procedure, obtained in 85% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 13.6 min, minor enantiomer t_r = 15.2 min, ee= 90%; $[\alpha]^{25}_D$= +78.2 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 2.7 Hz, 1H), 7.40 (dd, J = 8.8, 2.7 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 4.36 (ddt, J = 11.0, 6.9, 5.5 Hz, 1H), 2.72-2.61 (m, 2H), 1.89 (dp, J = 14.7, 7.4 Hz, 1H), 1.83-1.71 (m, 1H), 1.07 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 160.1, 135.7, 126.6, 126.2, 121.7, 119.6, 79.3, 42.2, 27.9, 9.2 ppm; HRMS (ESI) calculated for $C_{11}H_{12}ClO_2$ [M + H] 211.0520 found 211.0519.

(*R*)-6-bromo-2-ethylchroman-4-one (6)



Synthesized according the general procedure, obtained in 81% yield; oil; enantiomeric excess was determined by HPLC (Chiracel ODH),hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 14.4 min, minor enantiomer t_r = 15.9 min, ee= 89%; $[\alpha]^{25}_D$= +64.3 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.8, 2.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.32-4.24 (m, 1H), 2.65-2.52 (m, 2H), 1.81 (dp, J = 14.7, 7.4 Hz, 1H), 1.75-1.54 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 160.5, 138.5, 129.3, 122.2, 120.0, 113.7, 79.3, 42.1, 27.8, 9.2 ppm; HRMS (ESI) calculated for $C_{11}H_{12}BrO_2$ [M + H] 255.0015 found 255.0016.

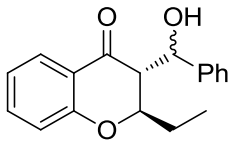
(*R*)-2-ethyl-7-methoxychroman-4-one (7)



Synthesized according the general procedure, obtained in 81% yield; oil; enantiomeric excess was determined by HPLC (Chiracel OJH),hexane:i-PrOH 99:1, 0.5 mL/min, minor enantiomer t_r = 28.9 min, minor enantiomer t_r = 30.3 min, ee= 92%; $[\alpha]^{25}_D$= +50.9 (c 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.8 Hz, 1H), 6.53 (dd, J = 8.8, 2.4 Hz, 1H), 6.40 (d, J = 2.3 Hz, 1H), 4.38-4.29 (m, 1H), 3.81 (s, 3H), 2.66-2.54 (m, 2H), 1.86 (dp, J = 14.7, 7.3 Hz, 1H), 1.80-1.68 (m, 1H), 1.05 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ

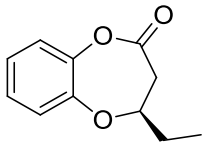
191.2, 166.0, 163.6, 128.6, 114.9, 109.7, 100.6, 79.4, 55.6, 42.2, 28.0, 9.3 ppm; HRMS (ESI) calculated for $C_{12}H_{15}O_3$ [M + H] 207.1016 found 207.1016.

(2*R*,3*R*)-2-ethyl-3-(hydroxy(phenyl)methyl)chroman-4-one (9)



$CuBr{\cdot}SMe_2$ (0.01 mmol, 2.02 mg) and **L4** (*R*,*S*)-Rev-Josiphos (0.012 mmol, 7.2 mg) were dissolved in dry DCM (2.0 mL) and the mixture was stirred at room temperature for 10 min. The mixture was cooled to -80 °C and subsequently the corresponding Grignard reagent solution (1.25 equiv.) was added dropwise. The reaction mixture was stirred at -80 °C for another 10 min. Then a solution of chromonone **2a** (0.4 mmol, 58.4 mg) in DCM (1.0 mL) was added slowly over 1h using a syringe pump. The reaction was stirred until TLC (*n*-pentane:EtOAc 9:1) showed full conversion. PhCHO (1.6 mmol, 150 µL) was added and the mixture was stirred at room temperature for 3 h. After that the reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL). The mixture was separated and the water layer was extracted with DCM (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under *vacuo*. Purification by flash chromatography over silica gel, using *n*-pentane:Et_2O 9:1 afforded the desired compound **9** was obtained as an oil (101.5 mg, 0.36 mmol, 90% yield, dr: 1:1.1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, J = 7.8, 1.5 Hz, 1H),7.75 (d, J = 7.8 Hz, 1H), 7.54-7.20 (m, 12H), 7.01 (t, J = 7.5 Hz, 1H), 6.99-6.92 (m, 3H), 5.15 (d, J = 6.7 Hz, 1H), 4.98* (d, J = 9.1 Hz, 1H), 4.72-4.63 (m, 1H), 4.04* (ddd, J = 9.4, 5.0, 2.3 Hz, 1H), 2.90 (dd, J = 6.6, 4.8 Hz, 1H), 2.73* (dd, J = 9.1, 2.3 Hz, 1H), 1.87-1.67 (m, 2H), 1.63-1.51 (m, 1H), 1.50-1.39* (m, 1H), 0.95 (t, J = 7.3 Hz, 3H), 0.84* (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.4, 159.6, 158.9, 141.4, 141.1, 136.6, 136.4, 128.7, 128.5, 128.43, 128.39, 128.0, 127.22, 127.0, 126.8, 126.8, 126.3, 121.3, 121.1, 118.20, 118.17, 79.7, 79.3, 72.9, 72.6, 57.9, 57.0, 25.1, 24.7, 9.84, 9.75 ppm; HRMS (ESI) calculated for $C_{18}H_{19}O_3$ [M + H] 283.1329 found 283.1328.

(*R*)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-2-one (10)



(*R*)-2-ethylchroman-4-one (**2a**) (0.25 mmol, 44.1 mg) and MCPBA (0.625 mmol, 107.9 mg) were dissolved in 5 mL of $ClCH_2CH_2Cl$, and the mixture was heated to 60 °C. The reaction mixture was stirred until TLC (*n*-pentane:EtOAc 9:1) showed full conversion and quenched with

saturated aqueous $NaHCO_3$ solution (10 mL) and 15 mL of DCM. The mixture was separated and the organic layer was washed with aq. $NaHCO_3$ (2×7 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under *vacuo*. Purification by flash chromatography over silica gel, using *n*-pentane:Et_2O 9:1 afforded the desired compound **10** as an oil (33.7 mg, 0.178 mmol, 71% yield); oil; enantiomeric excess was determined by HPLC (Chiracel ODH), hexane:i-PrOH 99:1, 0.5 mL/min, major enantiomer t_r = 30.9 min, minor enantiomer t_r = 23.7 min, ee= 93%; $[\alpha]^{25}_D$= +67.1 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.08 (m, 4H), 4.62-4.53 (m, 1H), 2.83 (dd, *J* = 13.2, 5.5 Hz, 1H), 2.65 (dd, *J* = 13.2, 7.5 Hz, 1H), 1.93-1.80 (m, 1H), 1.67-1.55 (m, 1H), 1.08 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 145.9, 144.8 126.7, 125.5, 124.1, 120.2, 84.0, 37.5, 27.5, 10.0 ppm; HRMS (ESI) calculated for $C_{11}H_{13}O_3$ [M + H] 193.0859 found 193.0858.

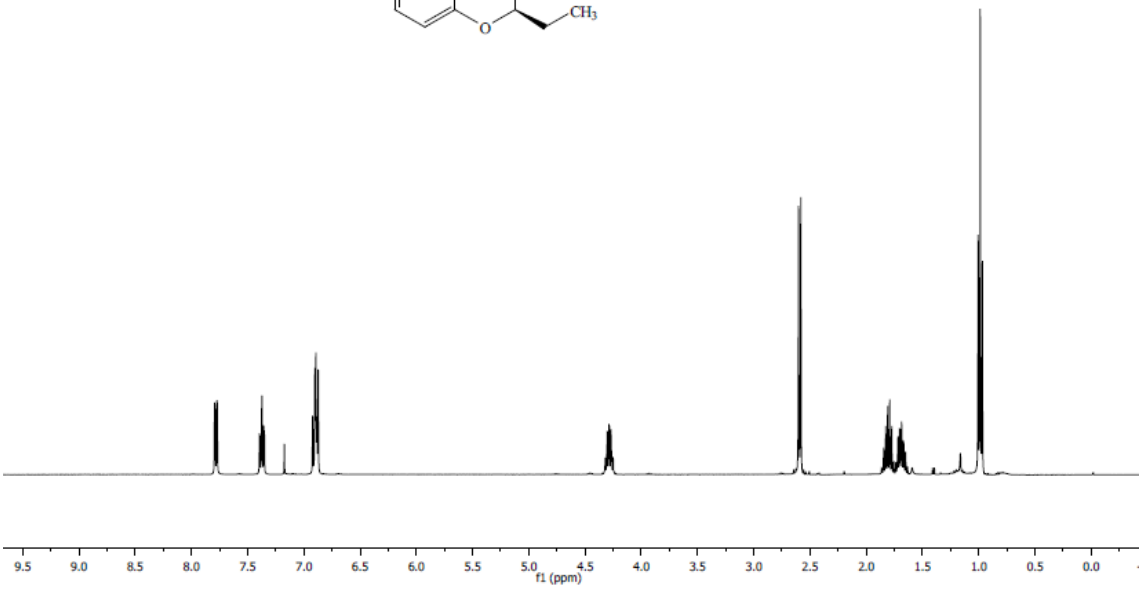
References:

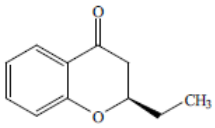
1-. L. Wang, X. Liu, Z. Dong, X. Fu, and X. Feng, *Angew. Chem. Int. Ed.* 2008, **47**, 8670.

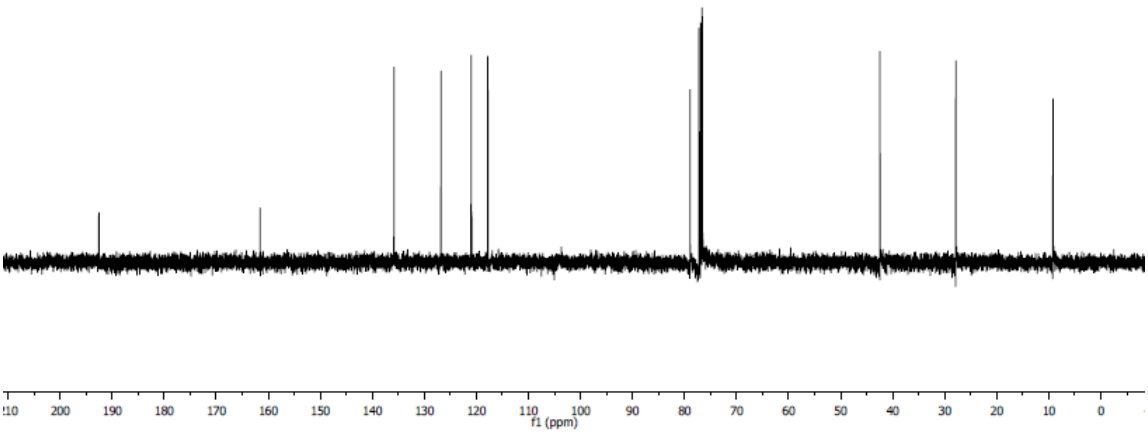
2-. M. M. Biddle, M. Lin and K. A.Scheidt, *J. Am. Chem. Soc.* 2007, **129**, 3830-3831.

NMR Spectra of Characterized Compounds

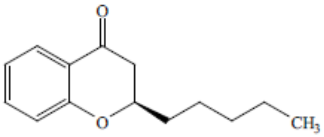
(*R*)-2-ethylchroman-4-one

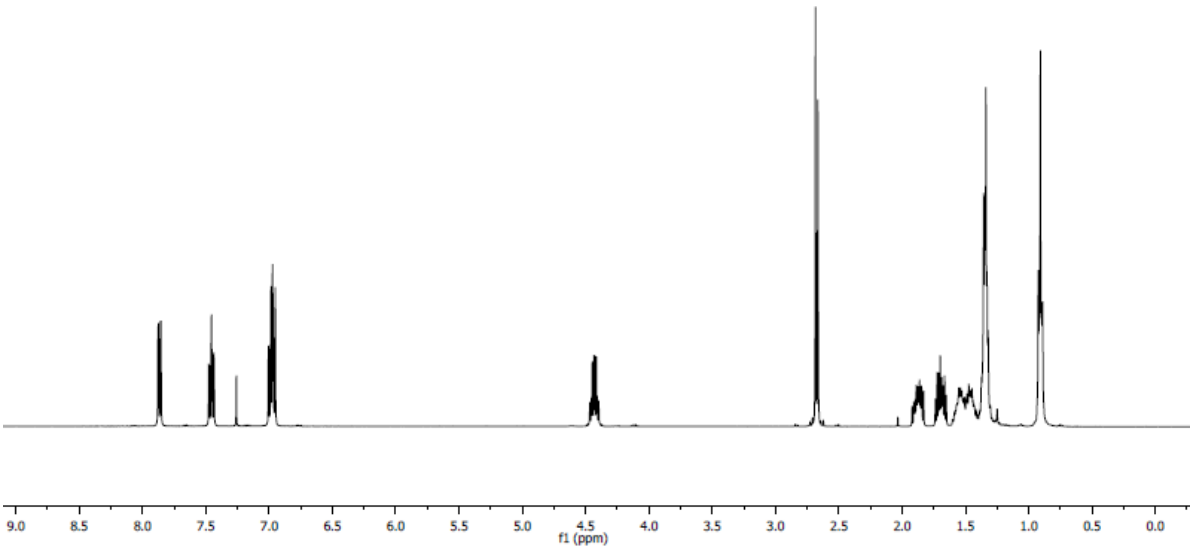


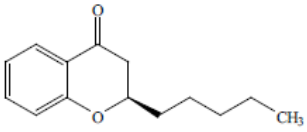


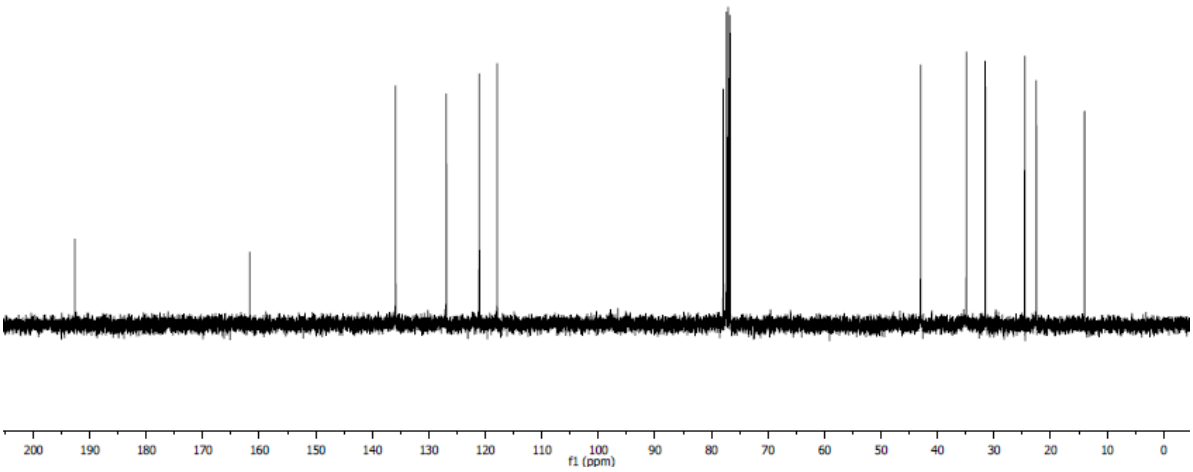


(R)-2-pentylchroman-4-one

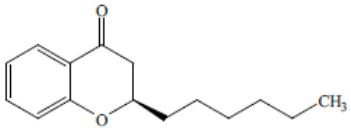


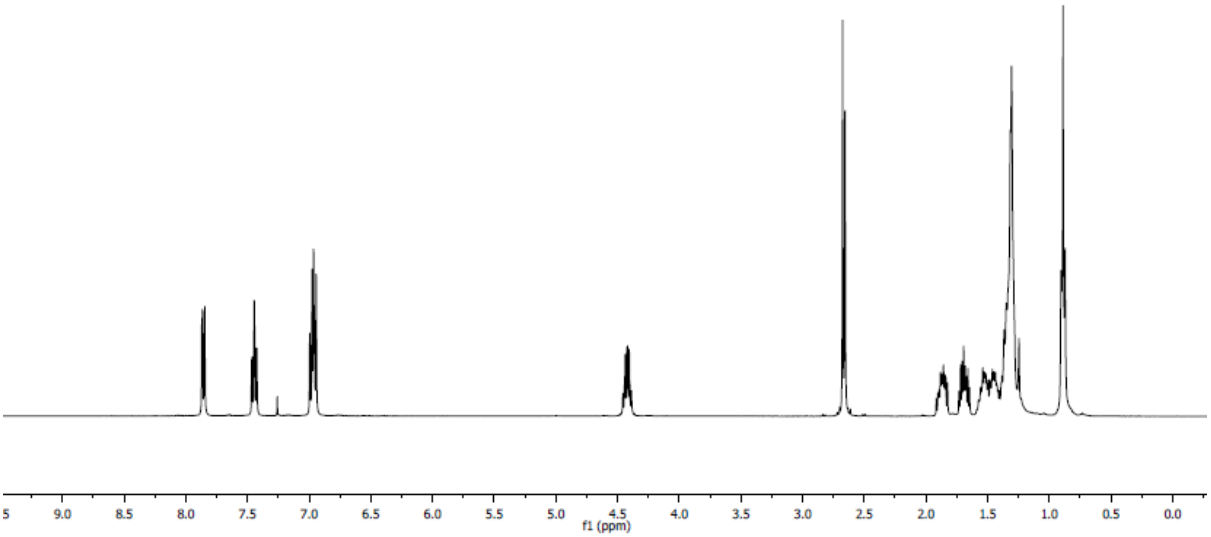


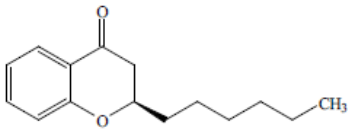


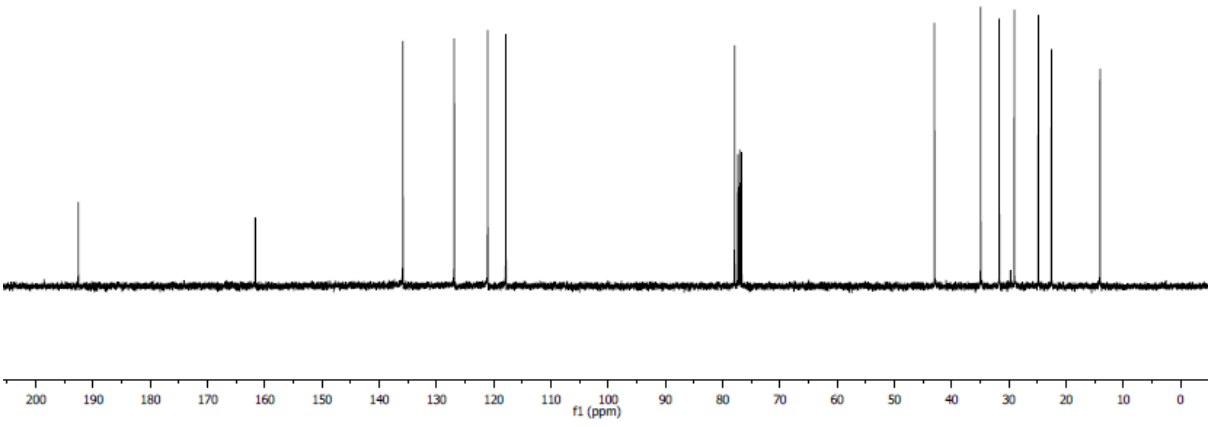


(R)-2-hexylchroman-4-one

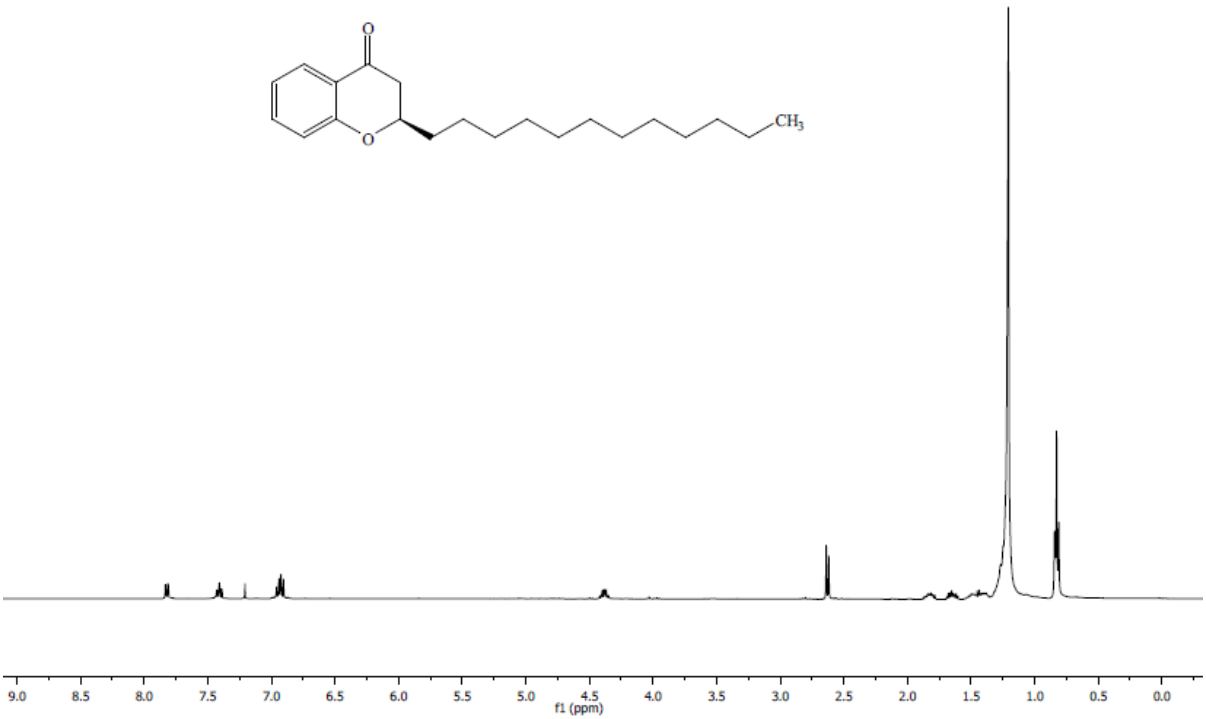


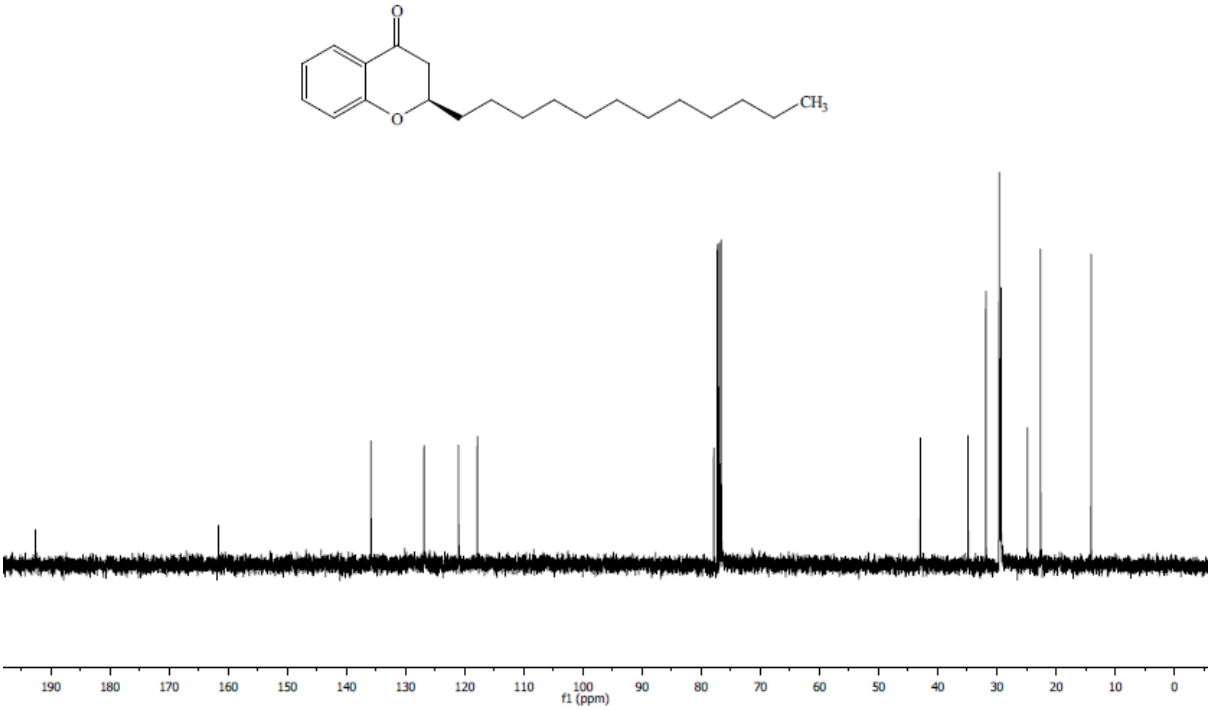




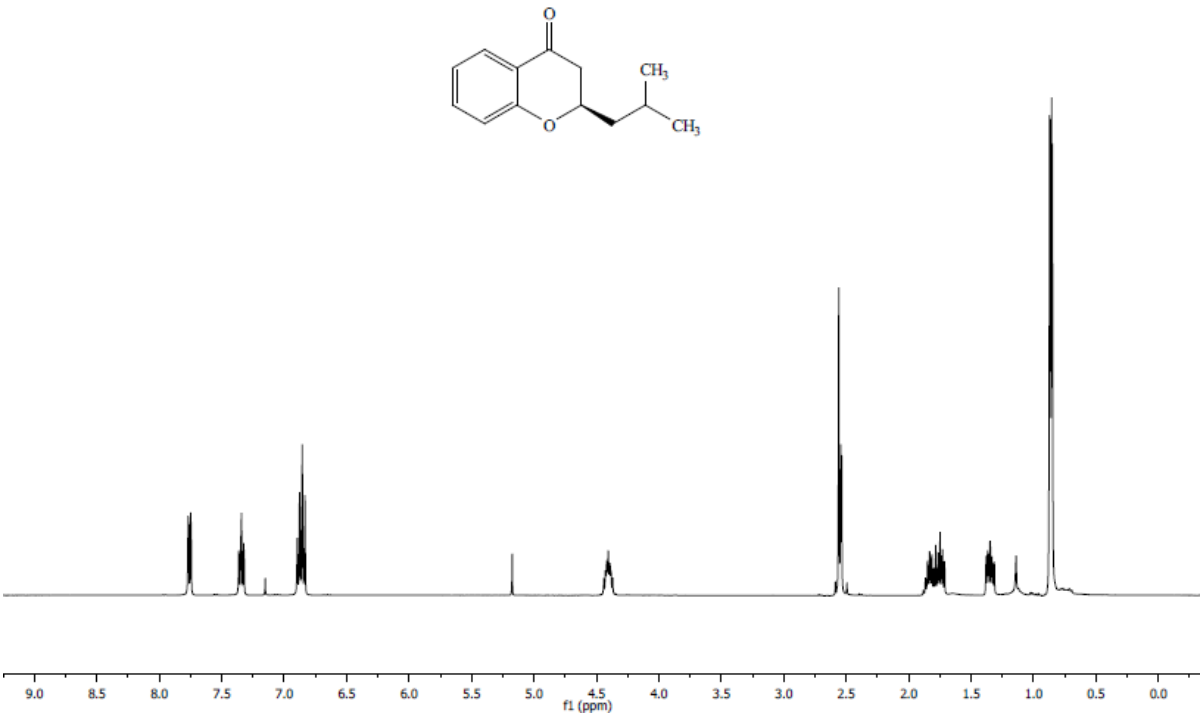


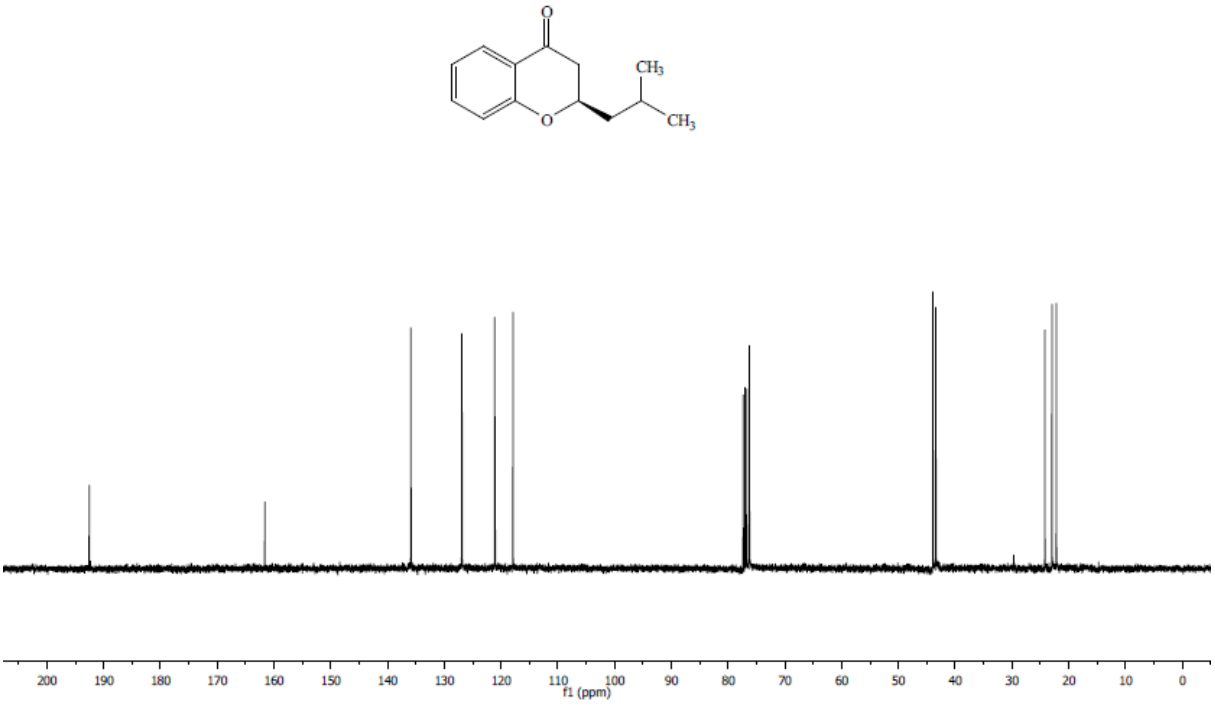
(R)-2-dodecylchroman-4-one



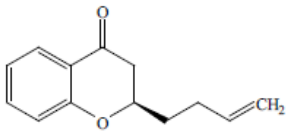


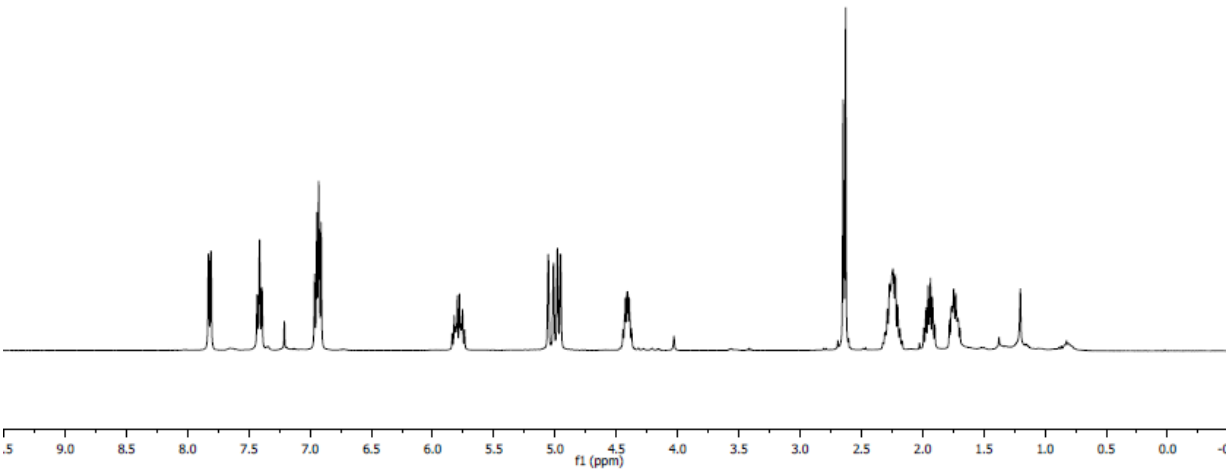
(*R*)-2-isobutylchroman-4-one

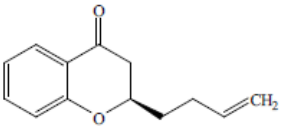


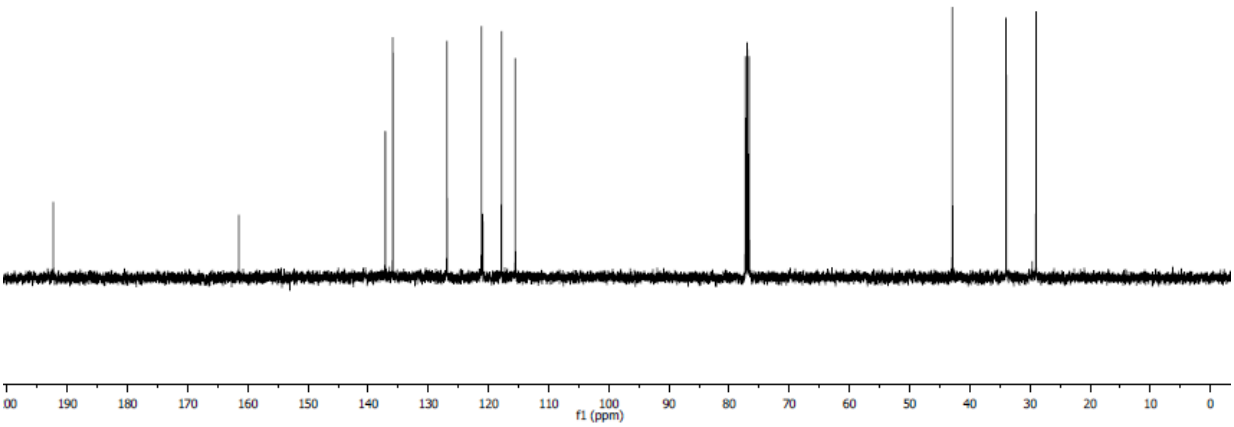


(R)-2-(but-3-en-1-yl)chroman-4-one

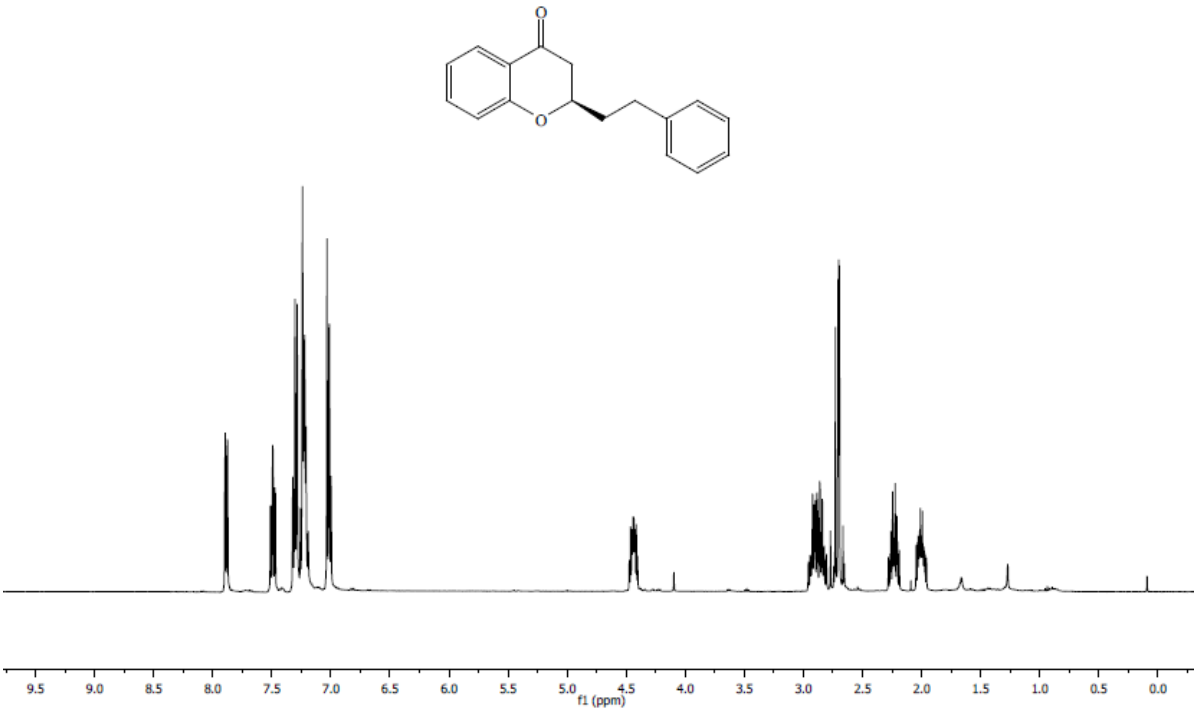


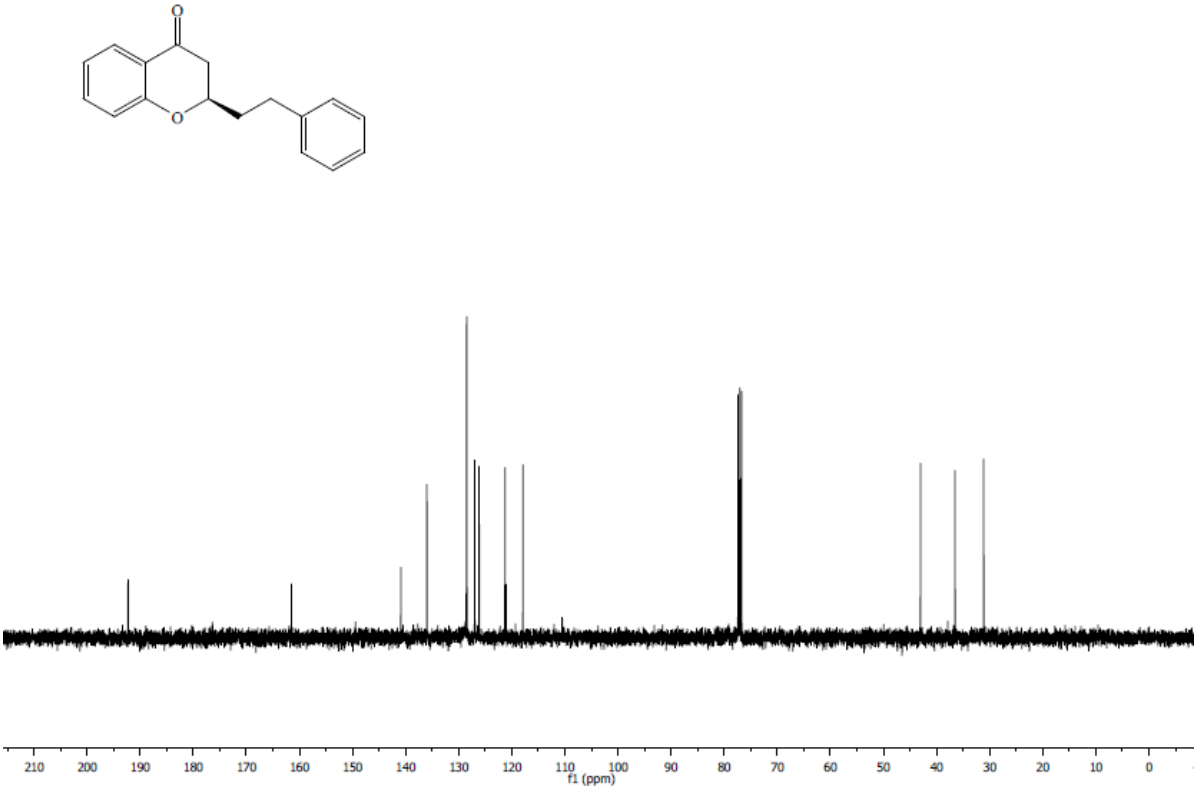




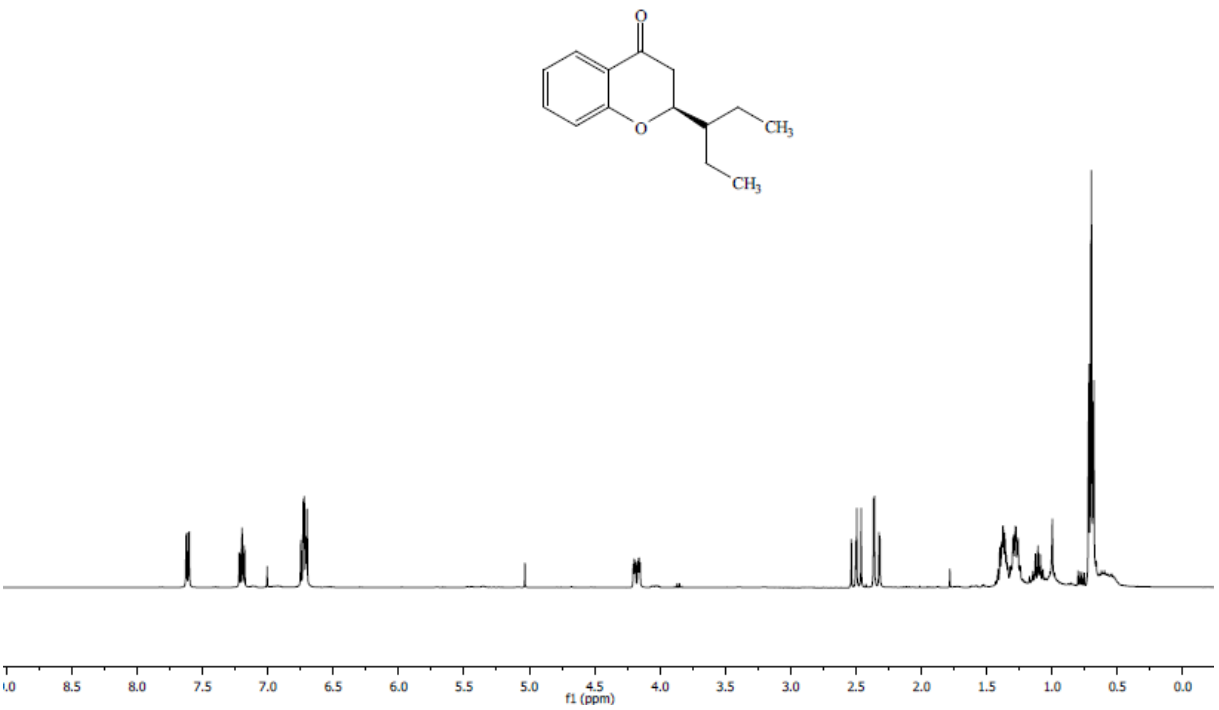


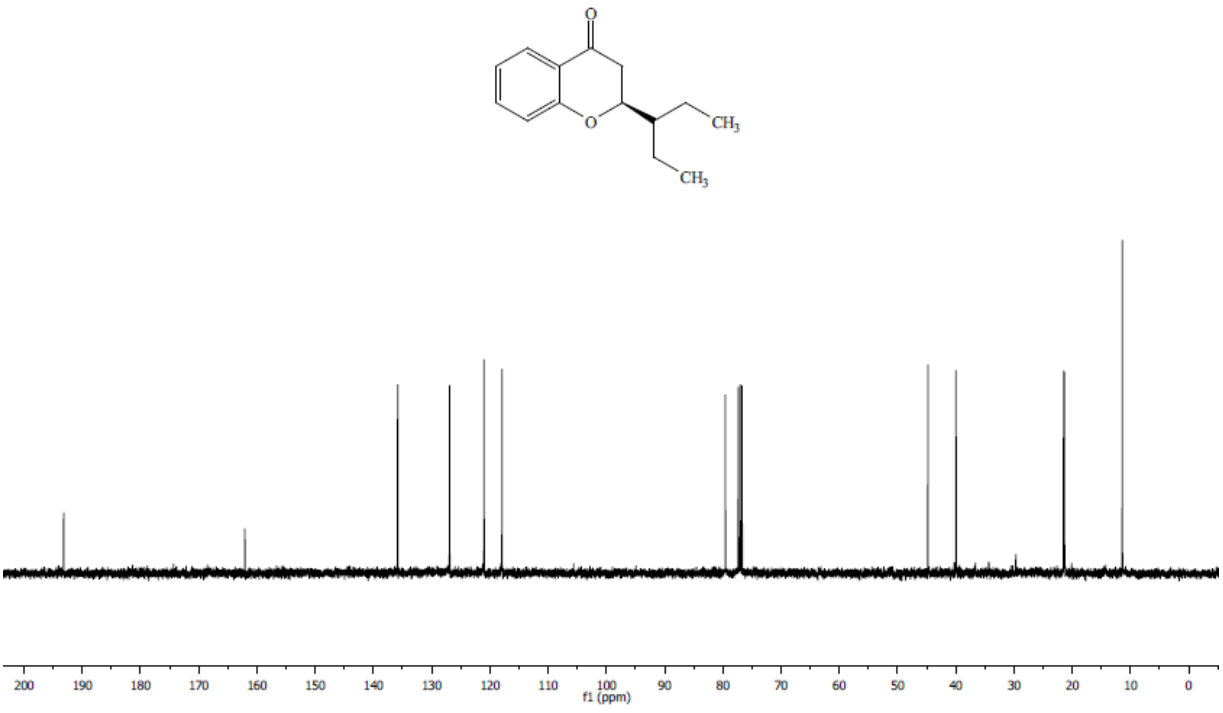
(*R*)-2-phenethylchroman-4-one



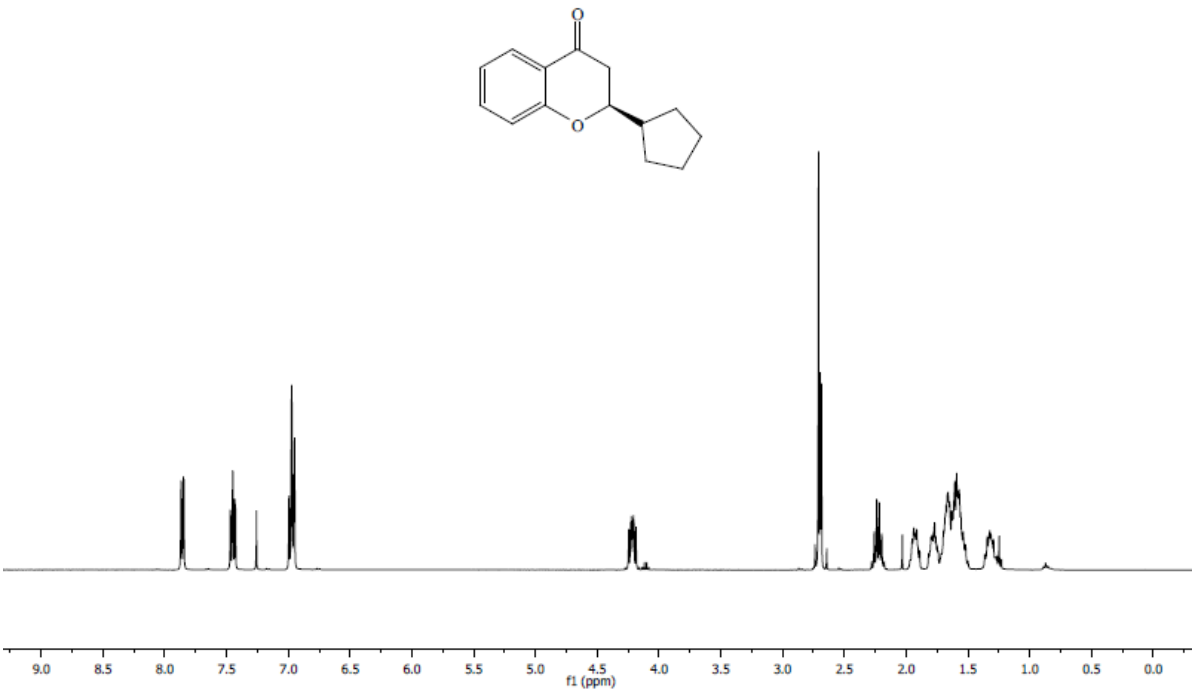


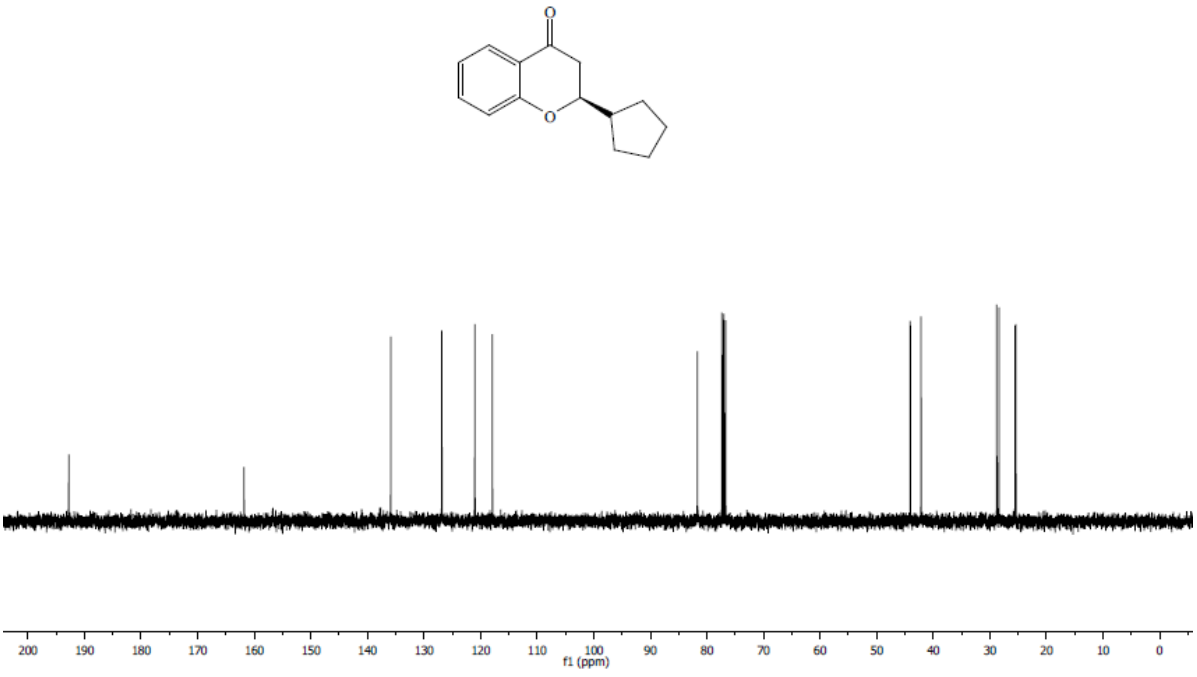
(*S*)-2-(pentan-3-yl)chroman-4-one



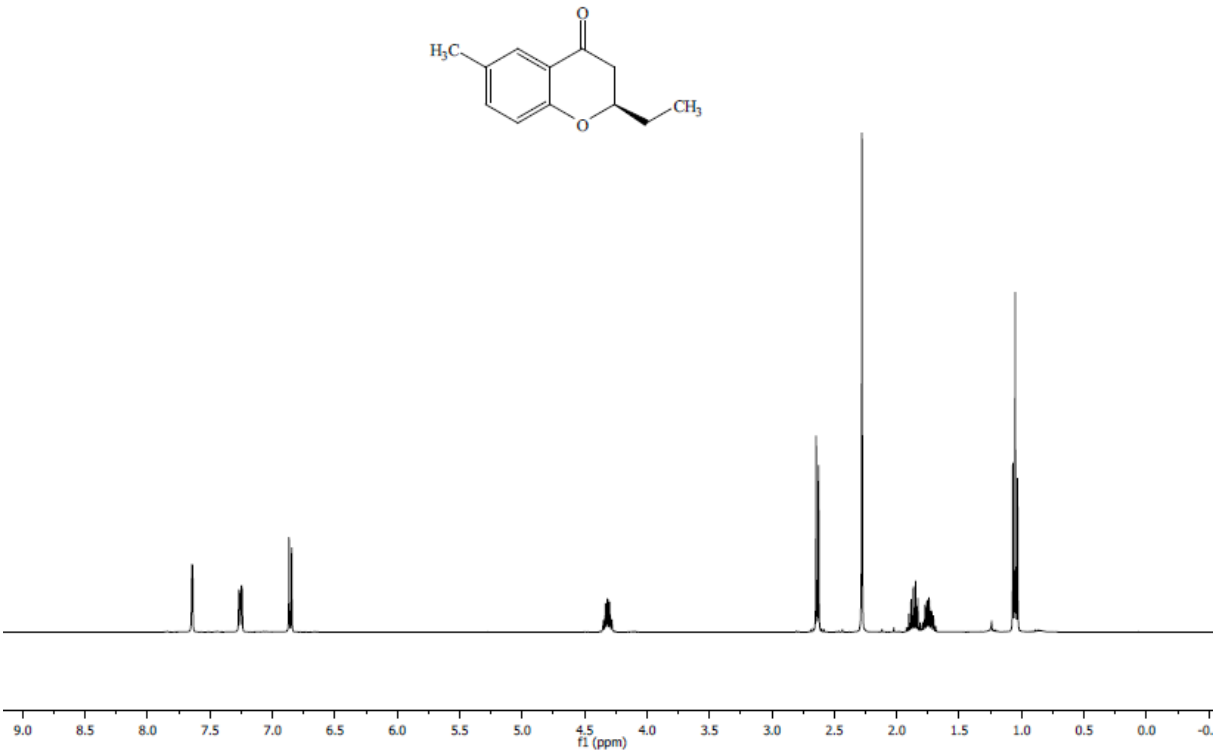


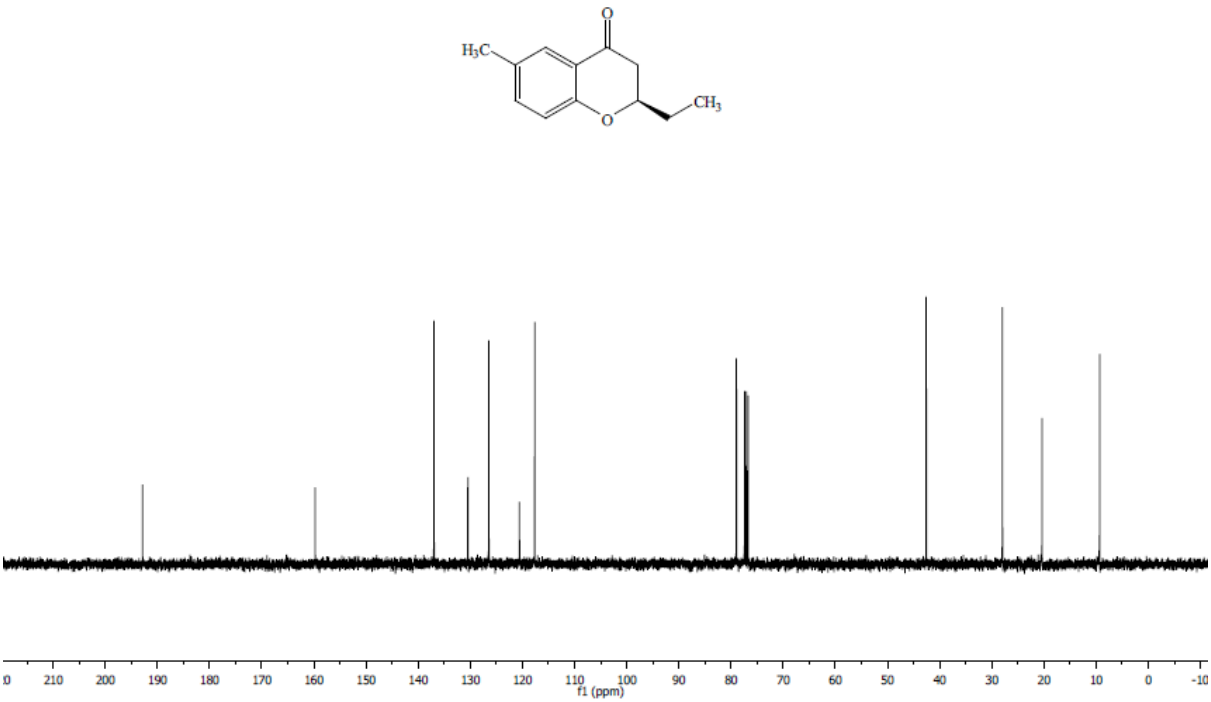
(*S*)-2-cyclopentylchroman-4-one



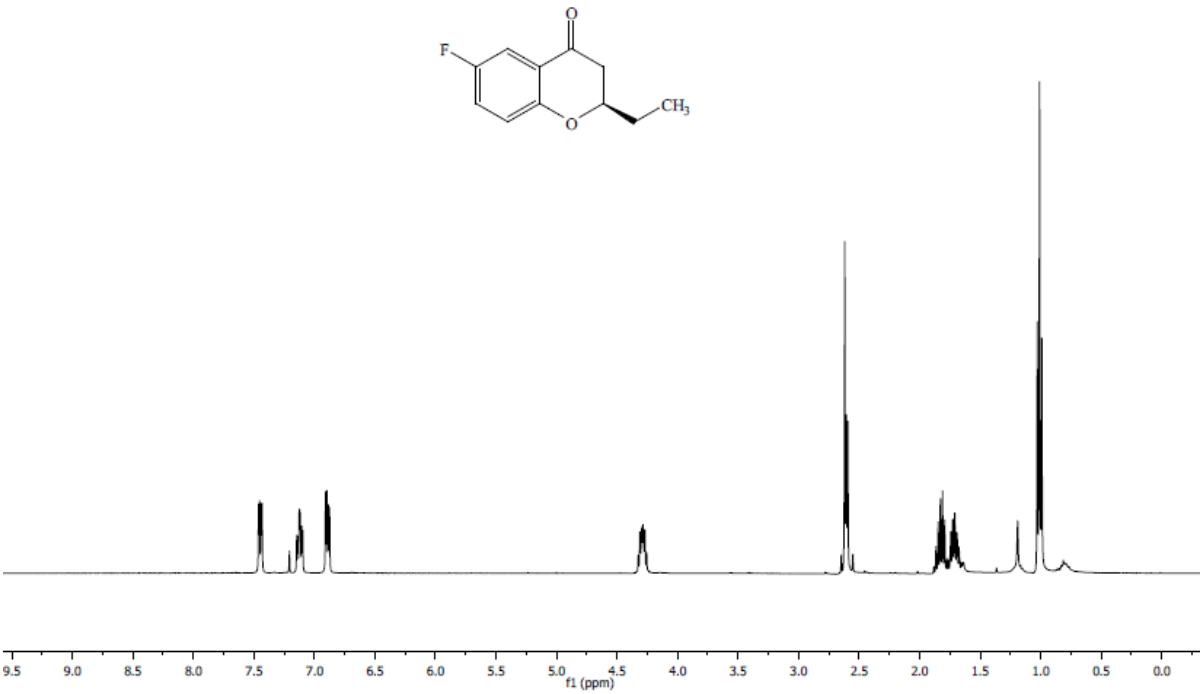


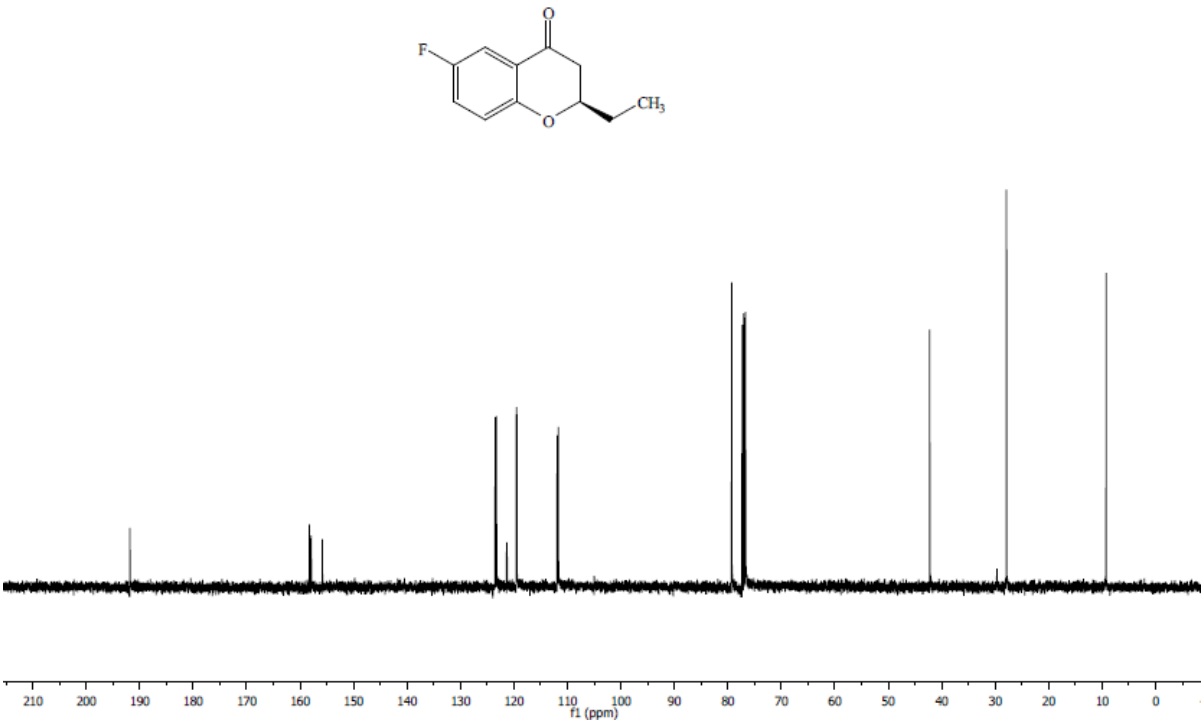
(*R*)-2-ethyl-6-methylchroman-4-one



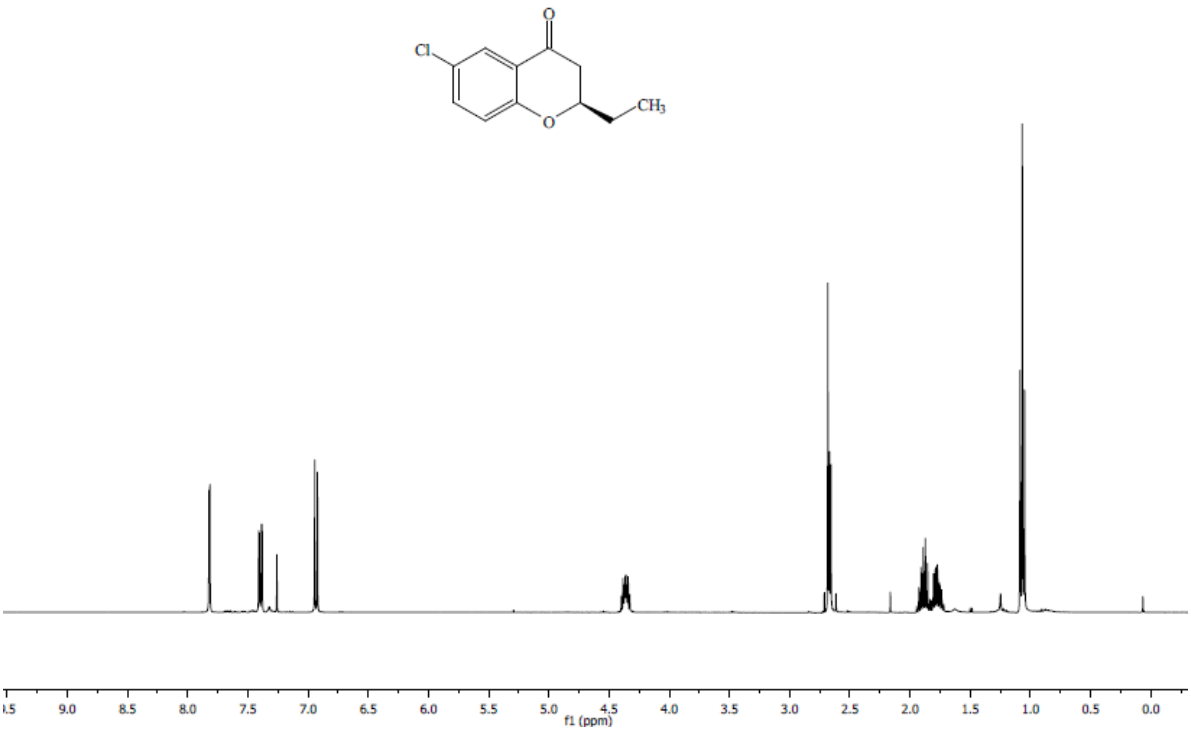


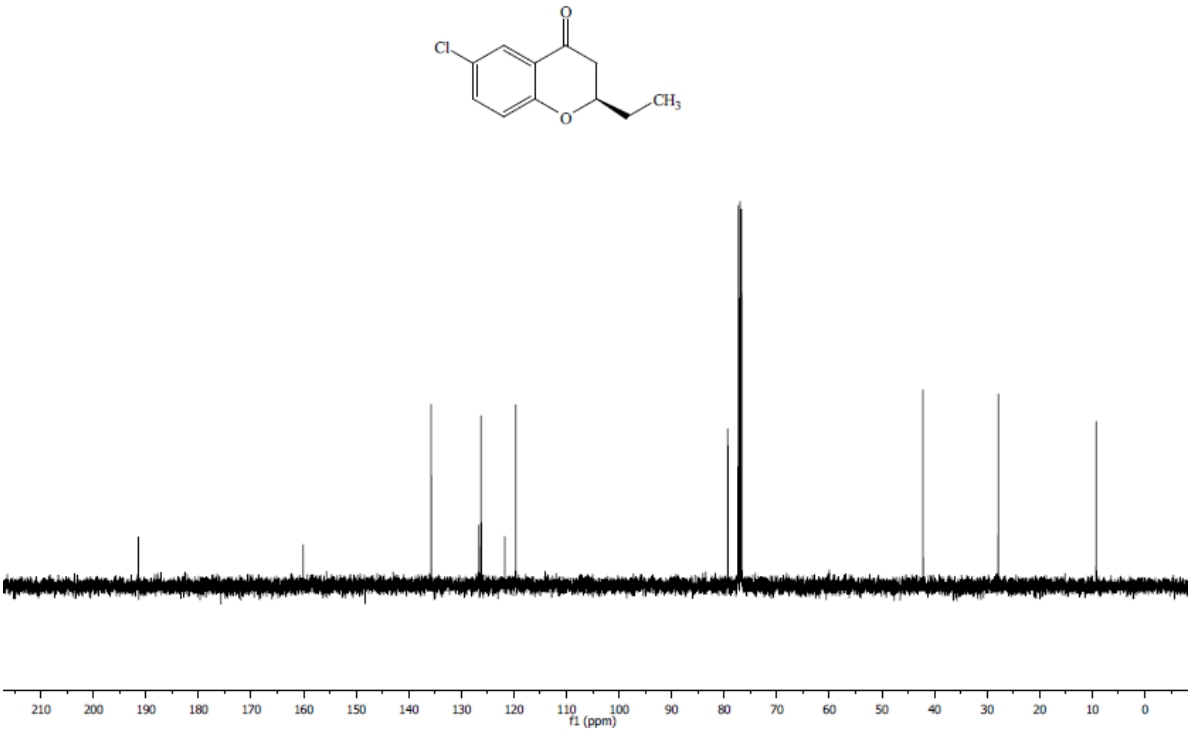
(*R*)-2-ethyl-6-fluorochroman-4-one



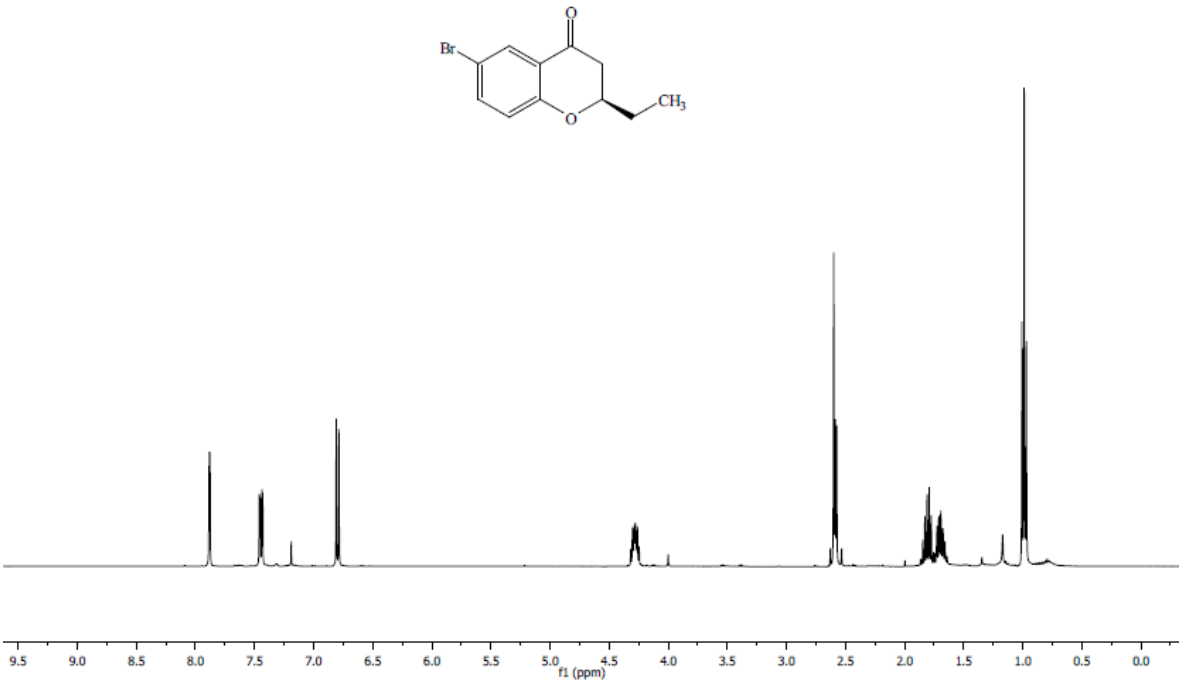


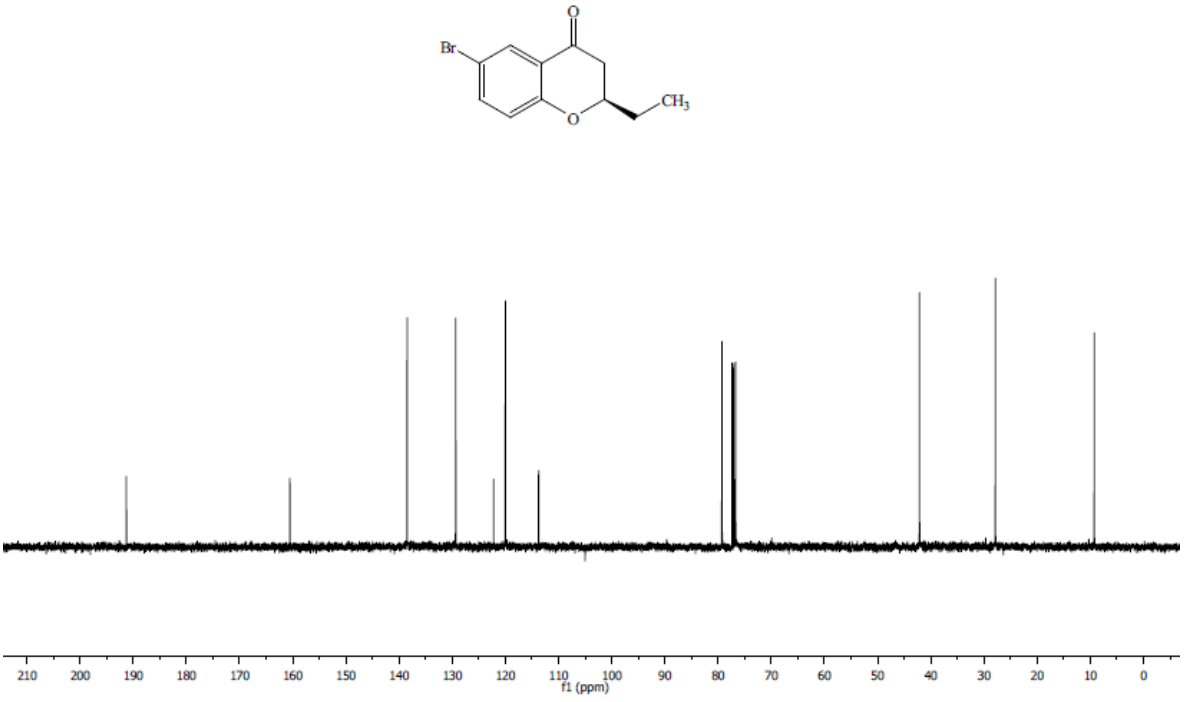
(*R*)-6-chloro-2-ethylchroman-4-one



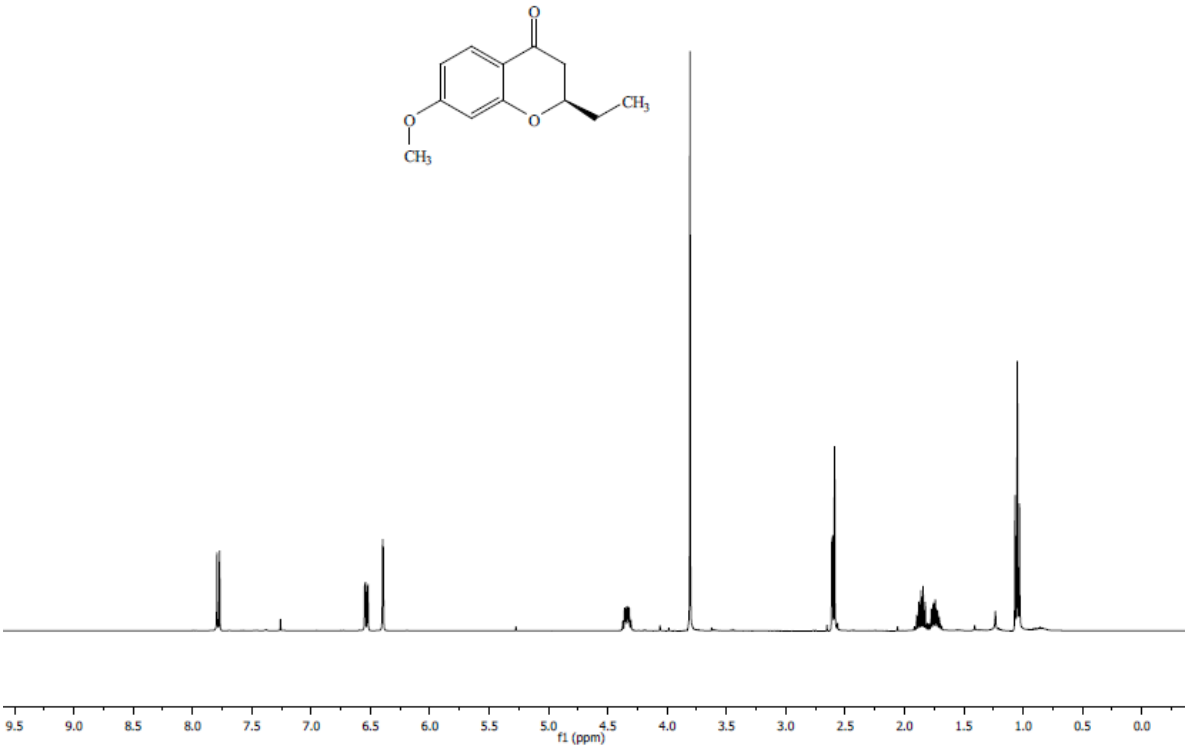


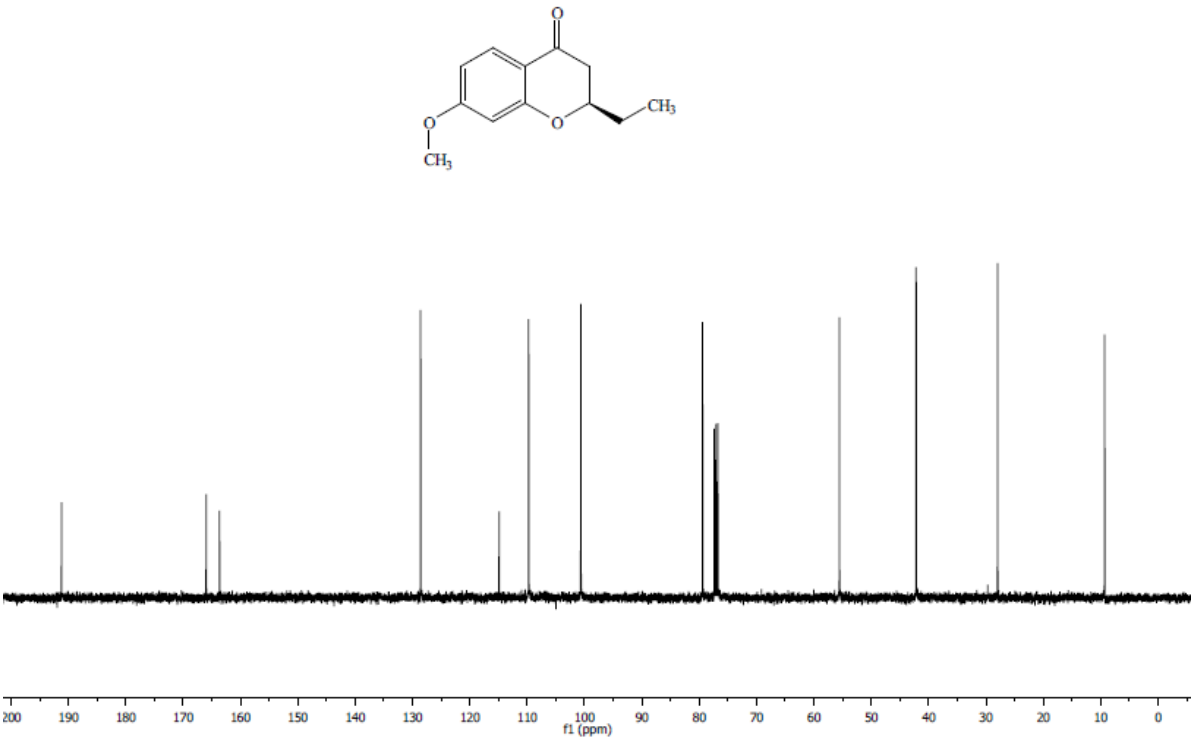
(*R*)-6-bromo-2-ethylchroman-4-one



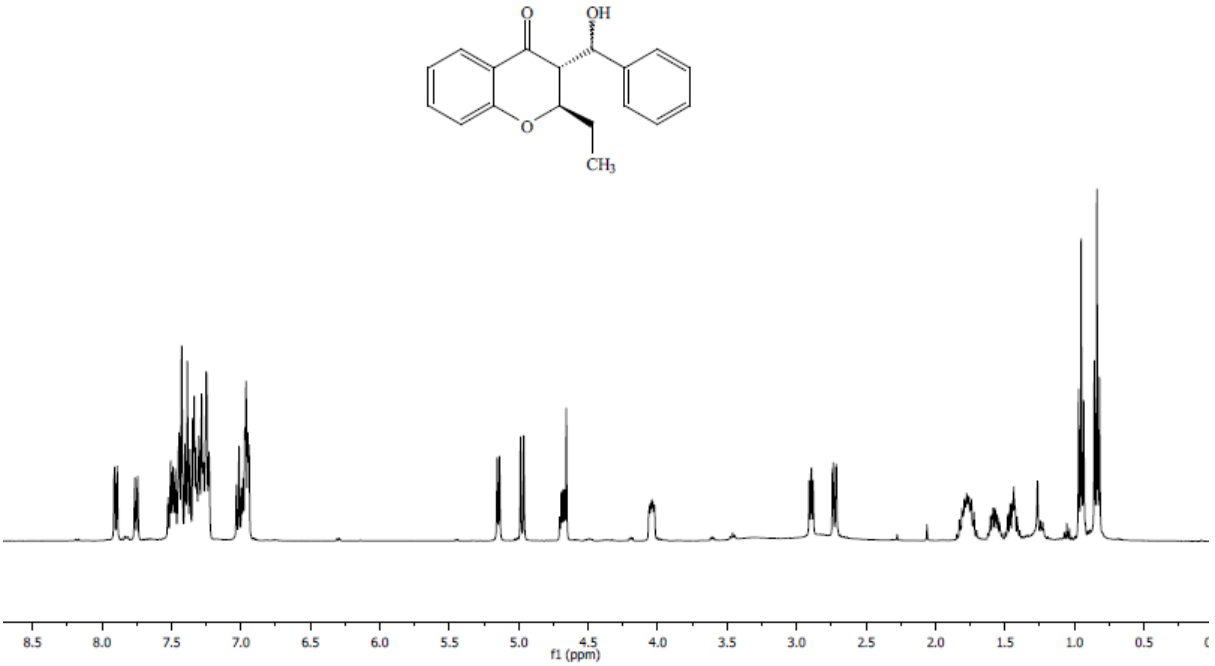


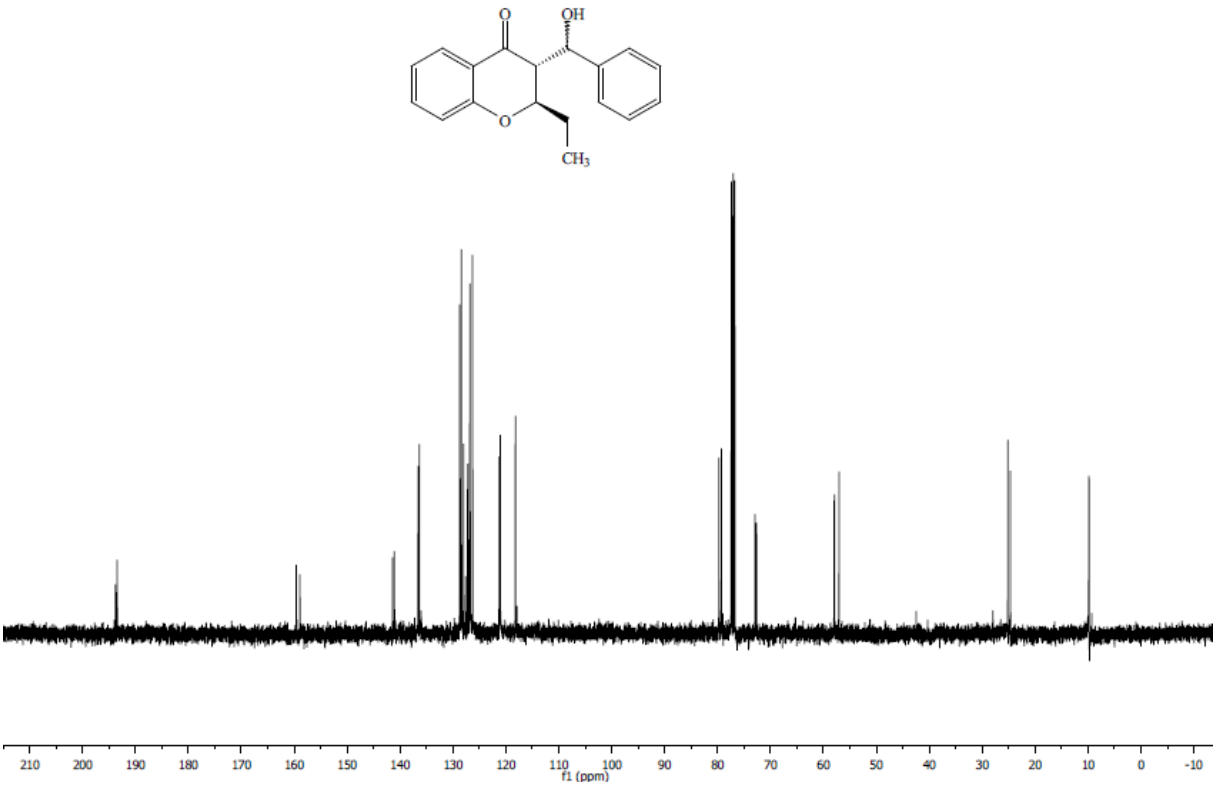
(*R*)-2-ethyl-7-methoxychroman-4-one



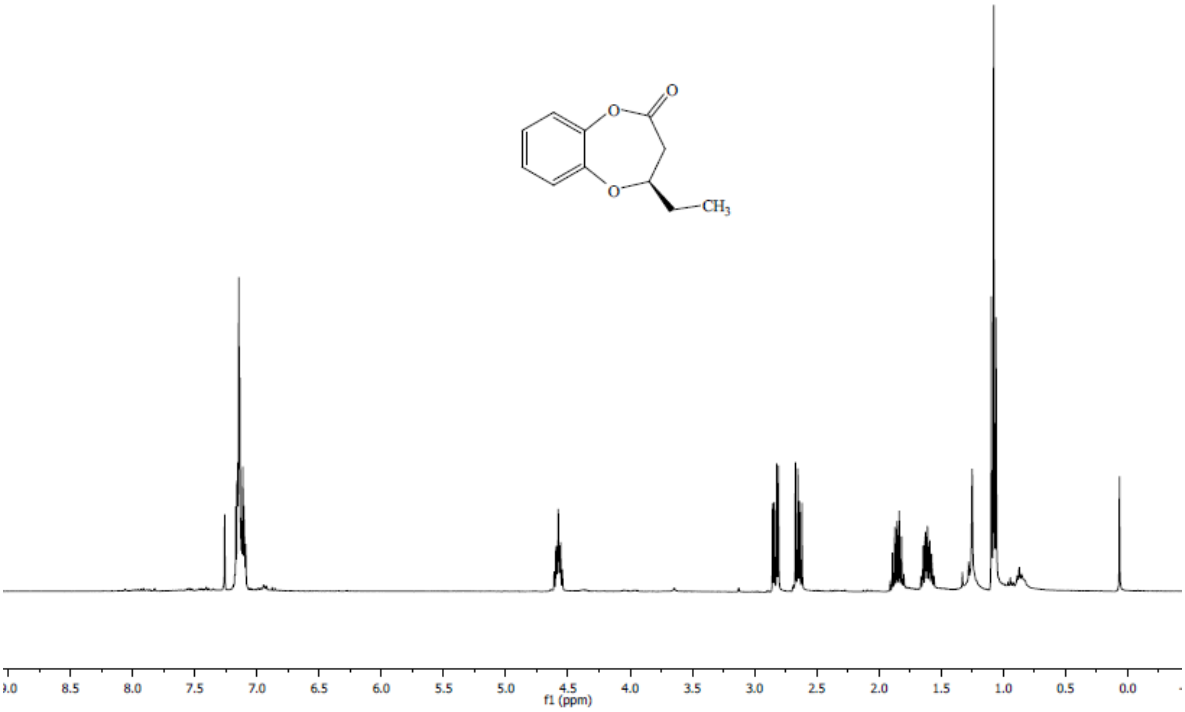


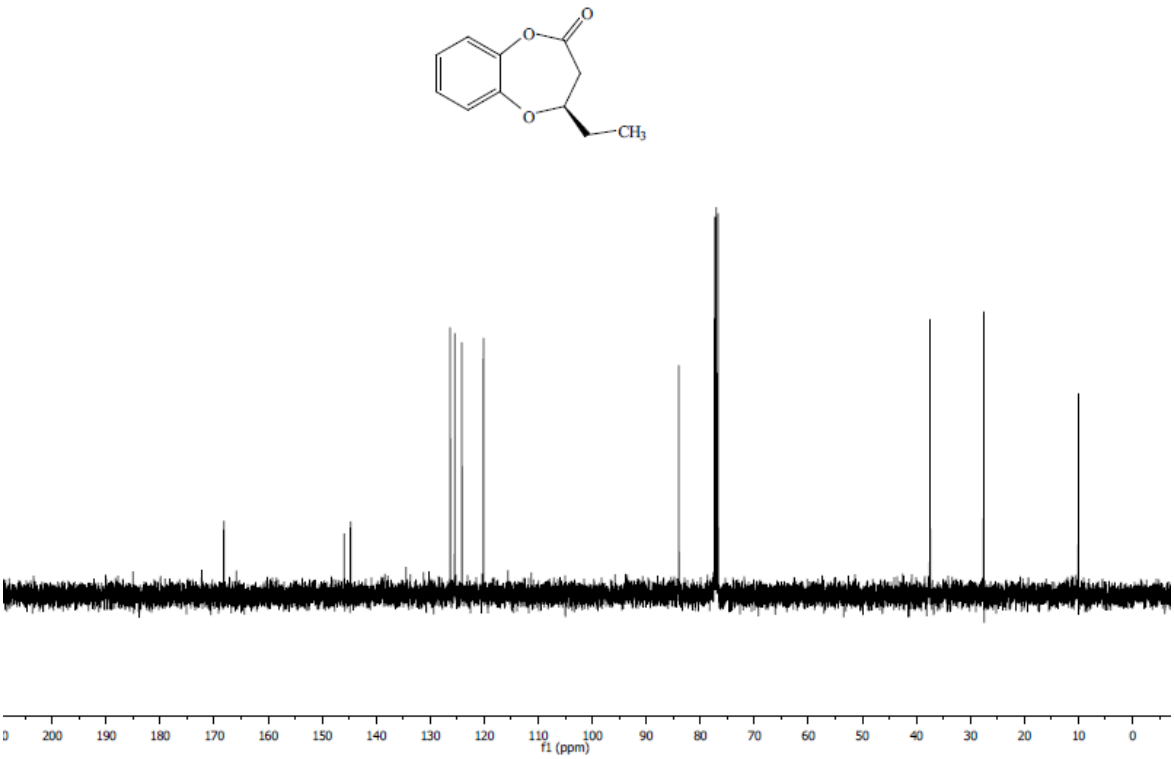
(2*R*,3*R*)-2-ethyl-3-(hydroxy(phenyl)methyl)chroman-4-one



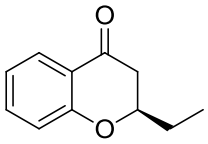


(*R*)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-2-one





HPLC data of the compounds



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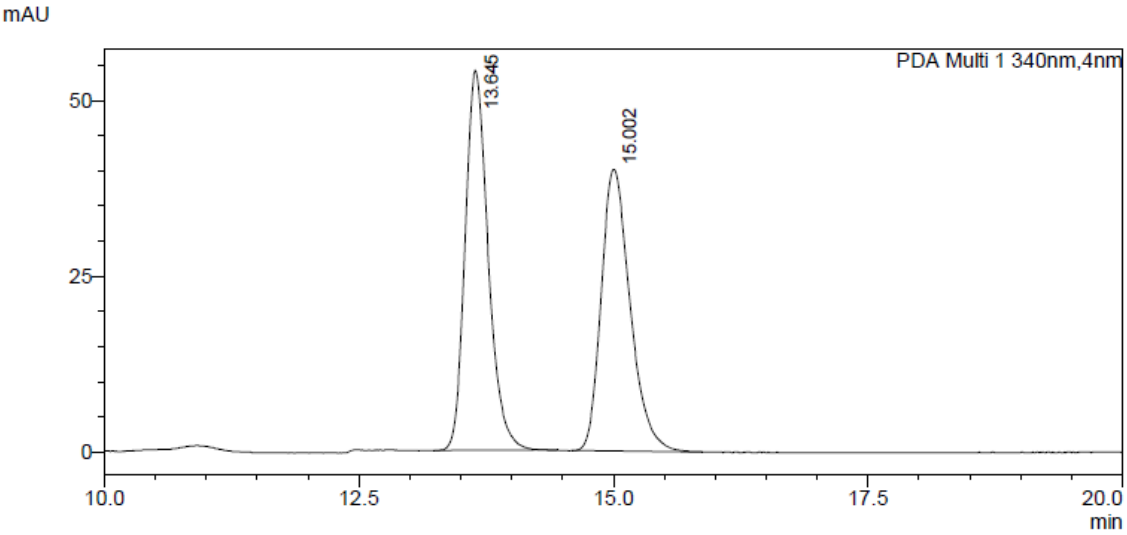
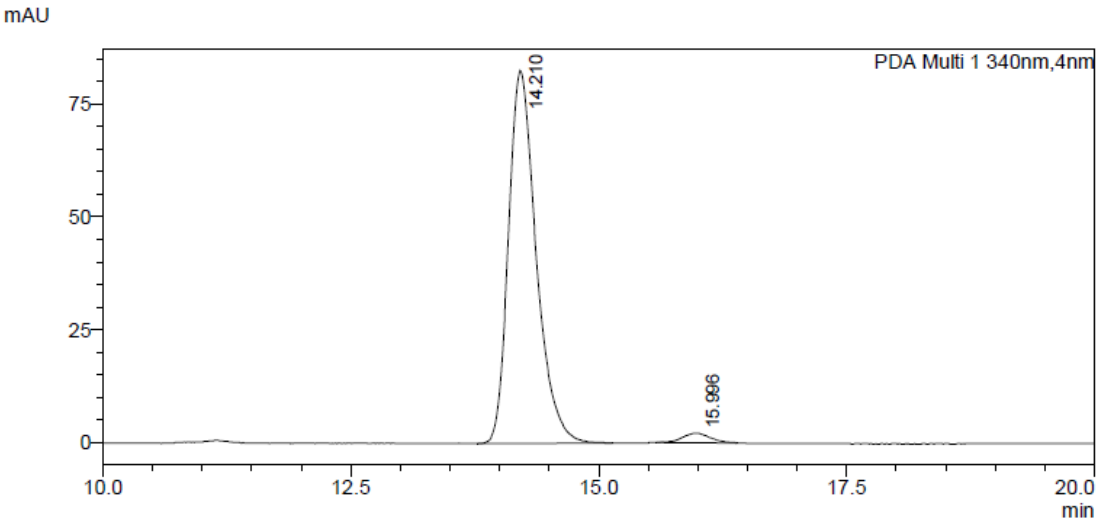


<Peak Table>

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.645	851567	54031	0.000		51.821
2	15.002	791717	40031	0.000		48.179
Total		1643284	94062			100.000

<Chromatogram>

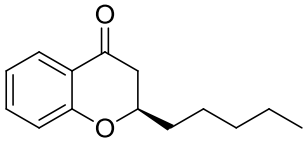


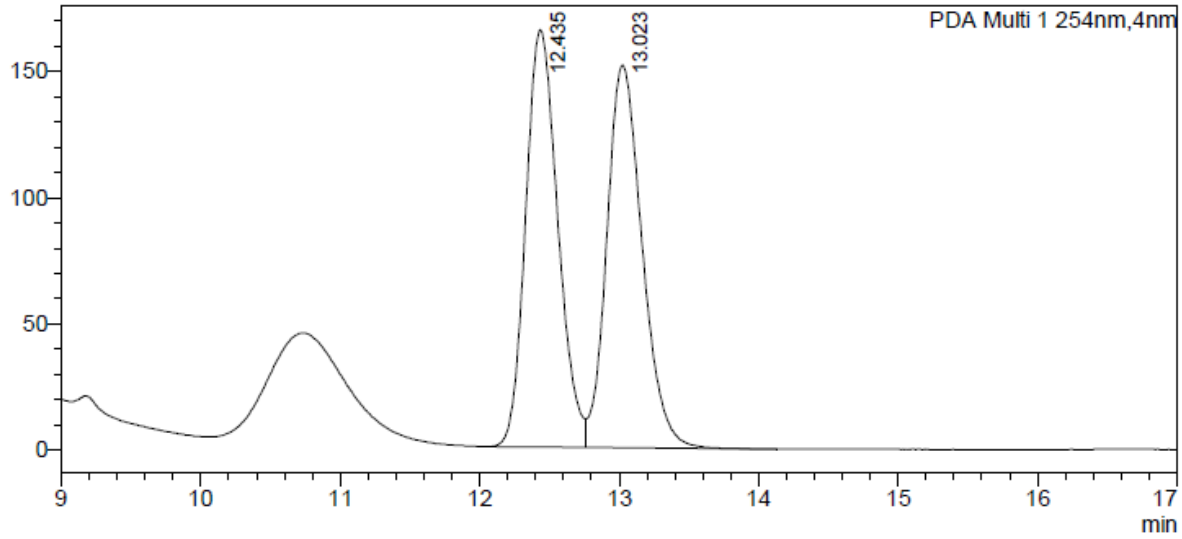
<Peak Table>

PDA Ch1 340nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	14.210	1603072	82510	0.000		97.562
2	15.996	40052	2089	0.000		2.438
Total		1643124	84599			100.000

UV Spectrum





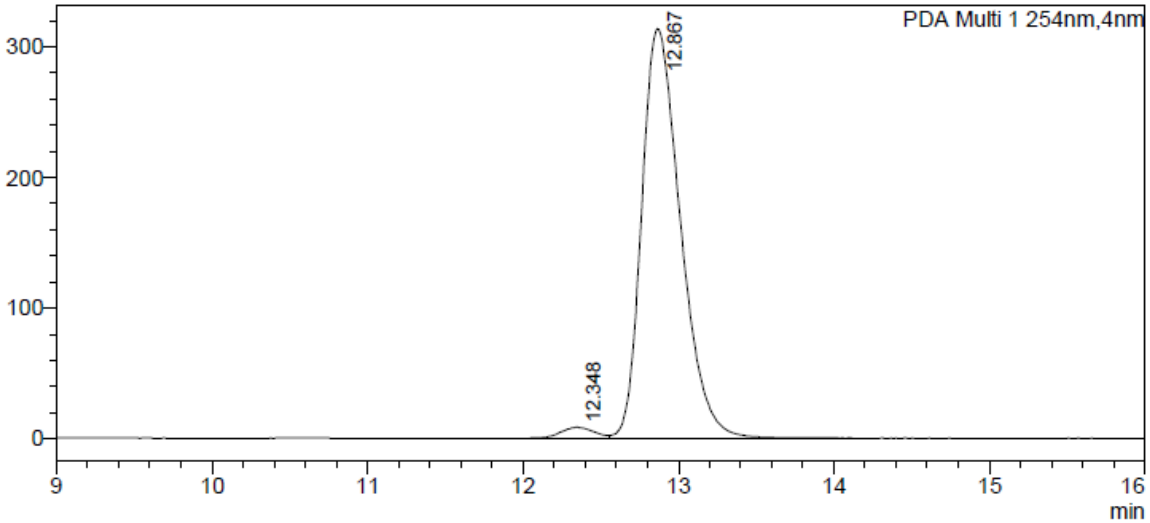
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.435	2653644	165283	0.000		49.840
2	13.023	2670653	151722	0.000		50.160
Total		5324297	317005			100.000

<Chromatogram>

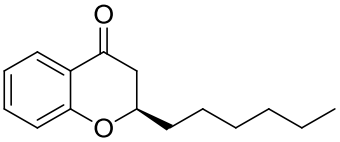
mAU



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.348	126546	8407	0.000		2.271
2	12.867	5446001	313573	0.000		97.729
Total		5572547	321980			100.000



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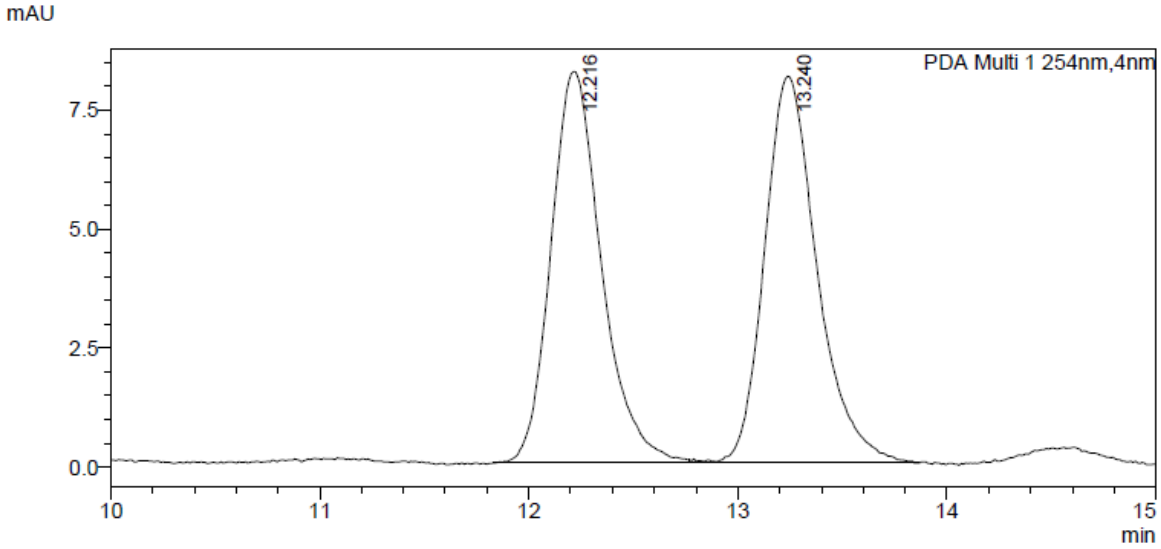
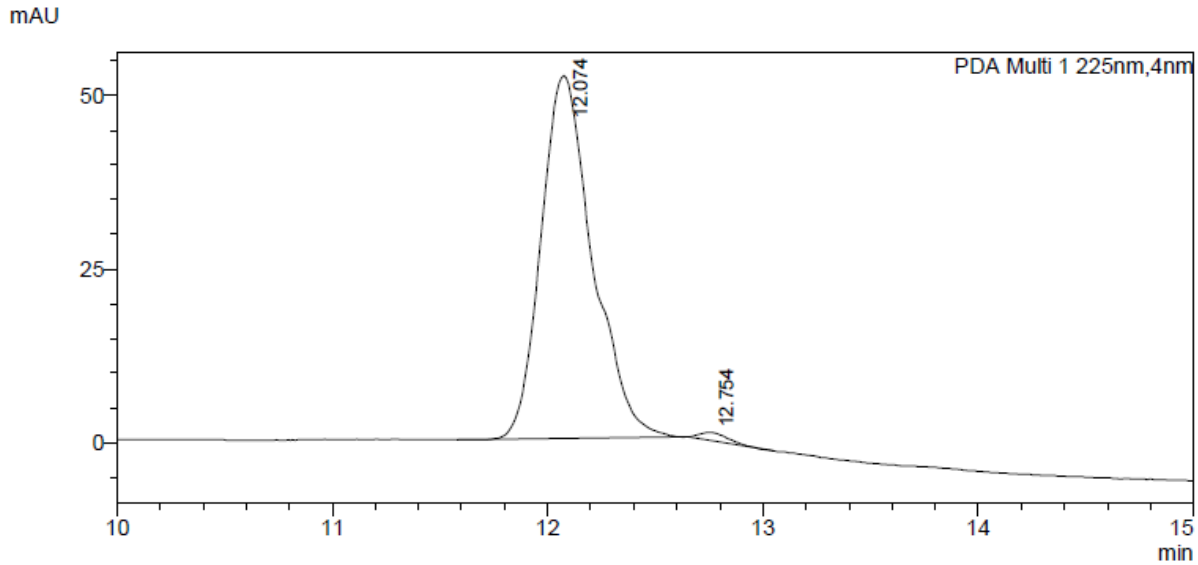


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.216	138569	8225	0.000		49.350
2	13.240	142217	8131	0.000		50.650
Total		280786	16357			100.000

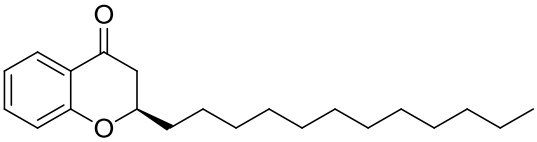
<Chromatogram>



<Peak Table>

PDA Ch1 225nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.074	868951	52237	0.000		98.871
2	12.754	9925	1154	0.000		1.129
Total		878876	53391			100.000



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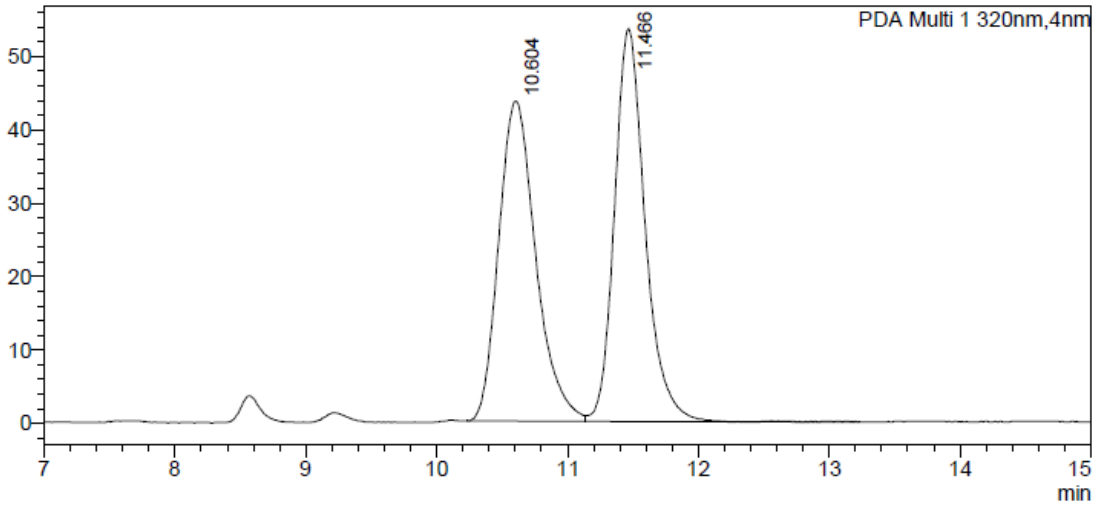
mAU



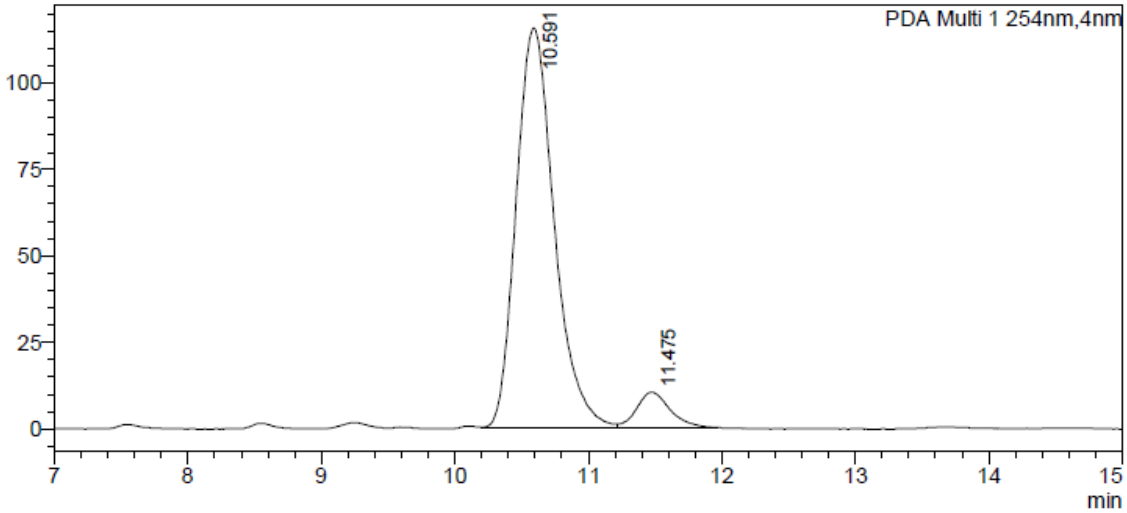
<Peak Table>

PDA Ch1 320nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	10.604	858504	43615	0.000		49.665
2	11.466	870074	53516	0.000		50.335
Total		1728578	97131			100.000

<Chromatogram>

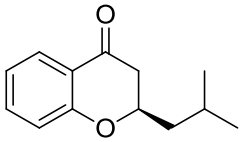
mAU



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	10.591	2288582	115504	0.000		92.783
2	11.475	178020	10274	0.000		7.217
Total		2466601	125778			100.000



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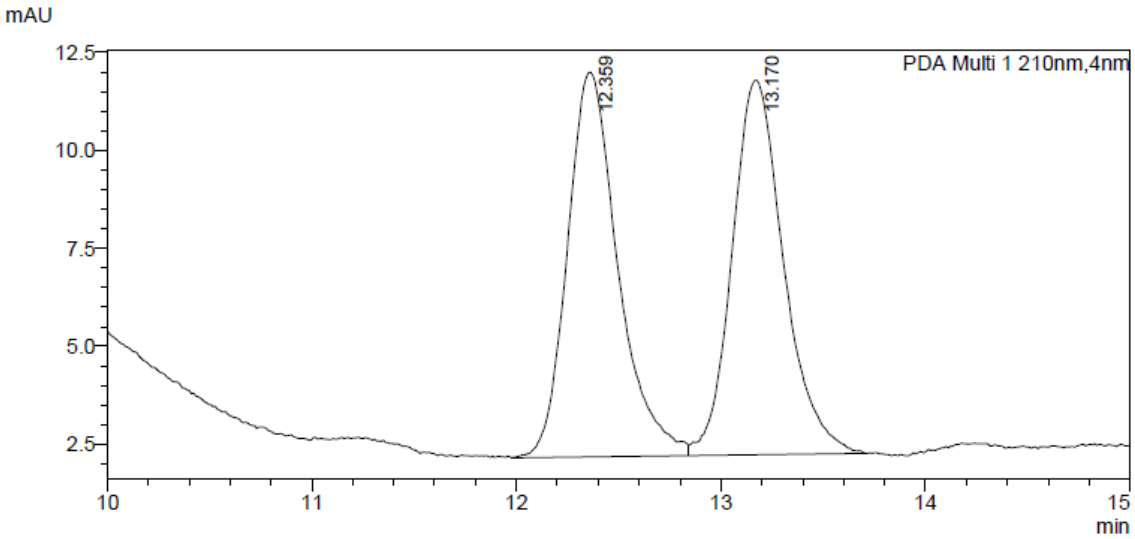
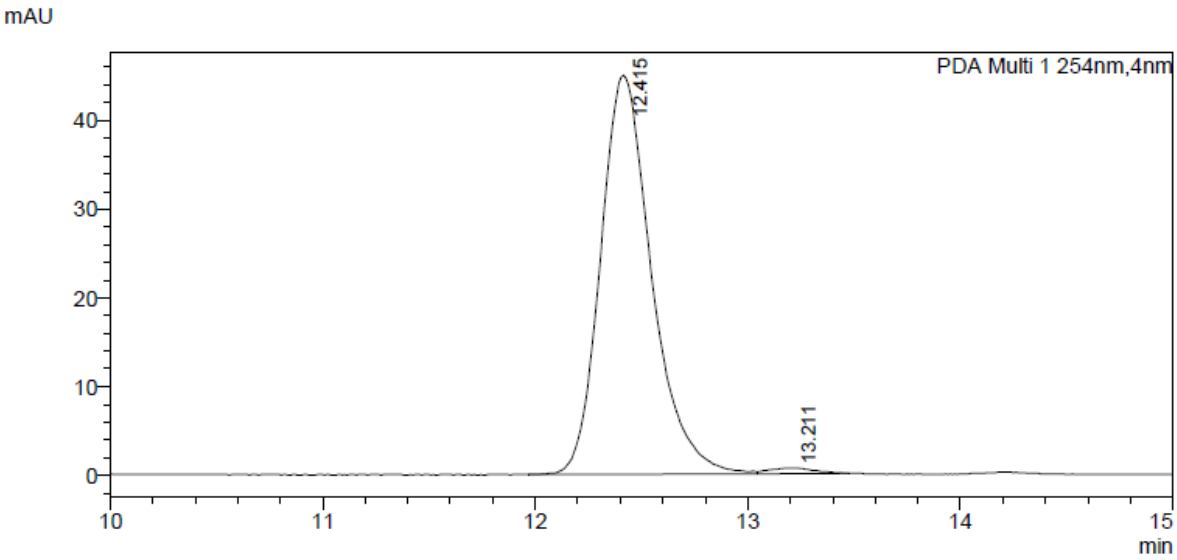


<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.359	168442	9813	0.000		50.141
2	13.170	167495	9563	0.000		49.859
Total		335937	19376			100.000

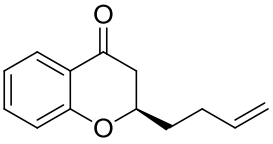
<Chromatogram>



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.415	750569	44950	0.000		98.790
2	13.211	9192	632	0.000		1.210
Total		759761	45582			100.000



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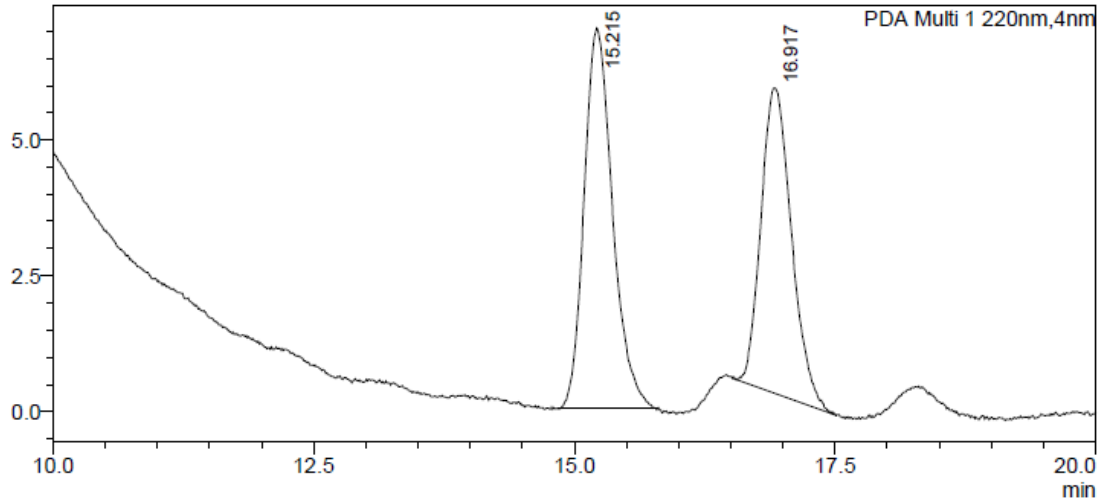

<Peak Table>

PDA Ch1 220nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	15.215	132949	6997	0.000		53.767
2	16.917	114322	5615	0.000		46.233
Total		247271	12612			100.000

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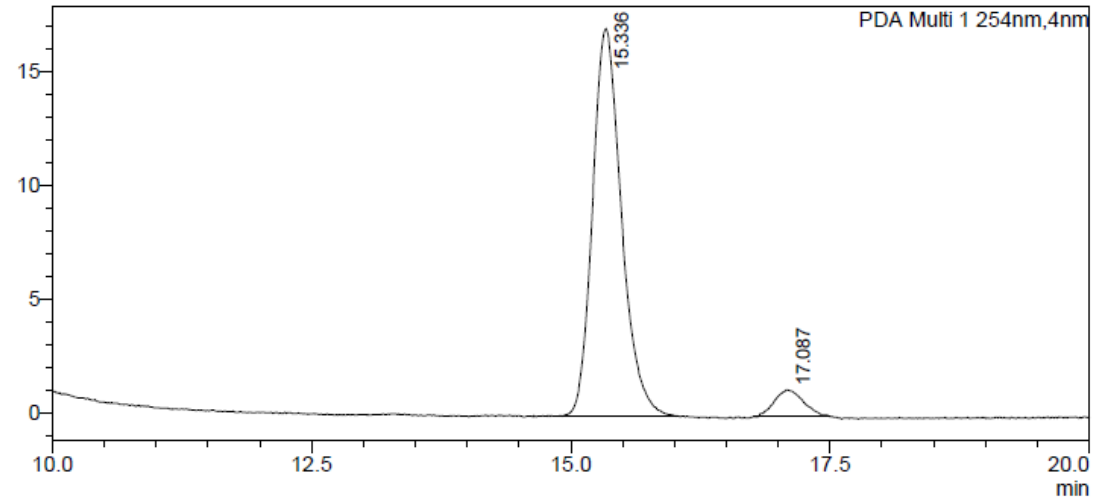
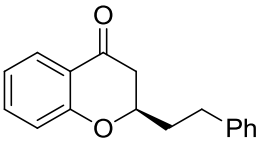
mAU



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	15.336	330494	17034	0.000		93.699
2	17.087	22226	1160	0.000		6.301
Total		352720	18195			100.000



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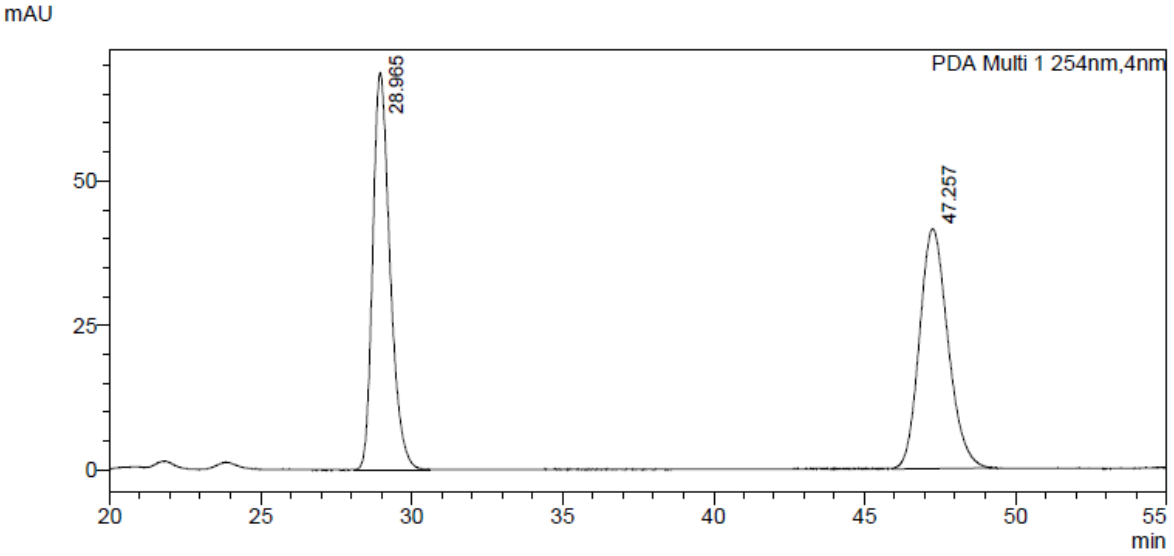

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	28.965	2731946	68724	0.000		50.055
2	47.257	2725920	41516	0.000		49.945
Total		5457866	110239			100.000

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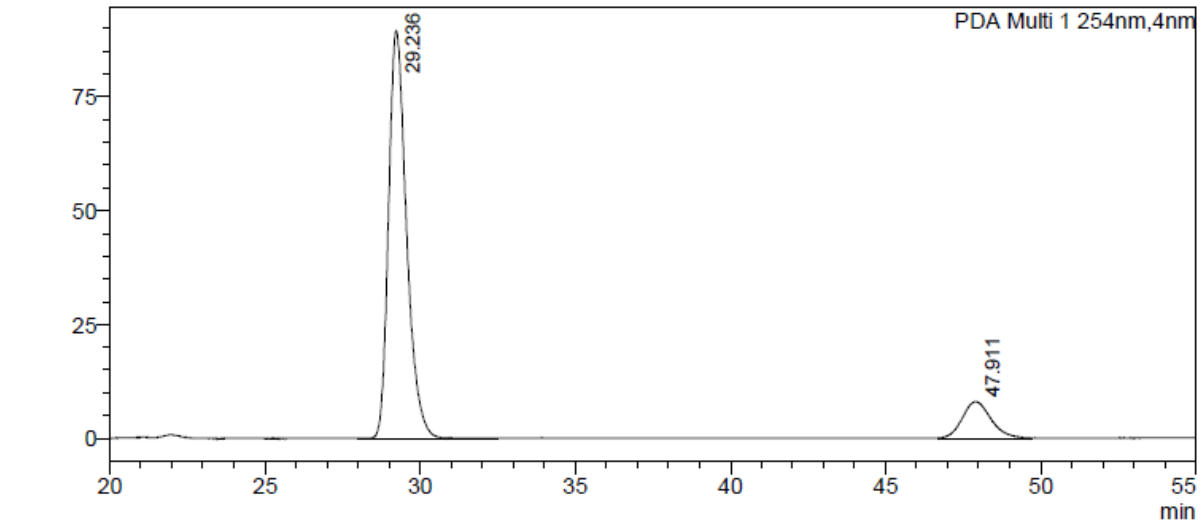
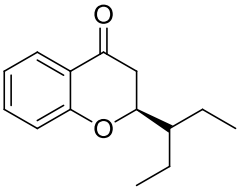


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	29.236	3593665	89448	0.000		87.532
2	47.911	511873	7987	0.000		12.468
Total		4105538	97434			100.000



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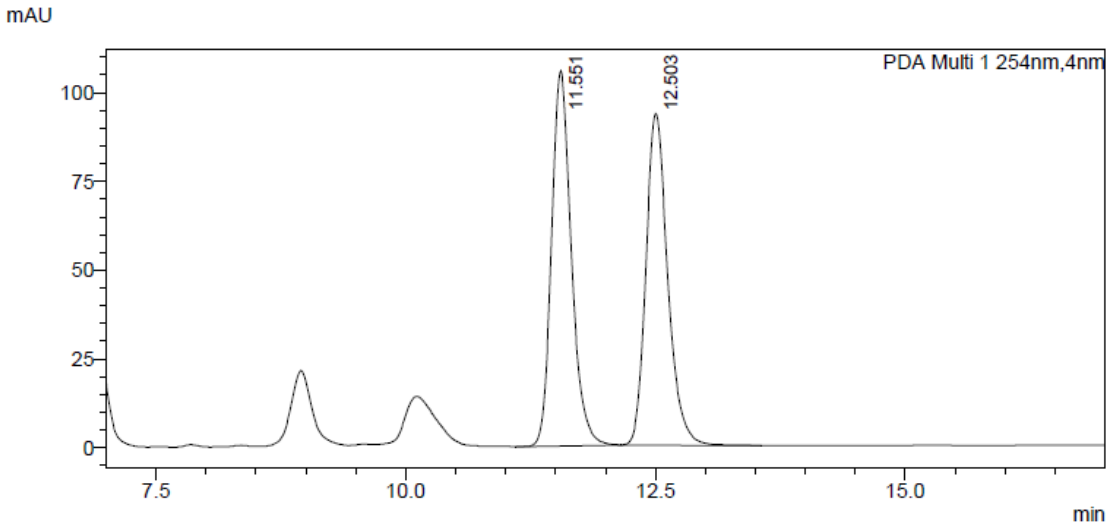

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	11.551	1453356	105572	0.000		50.662
2	12.503	1415357	93426	0.000		49.338
Total		2868713	198998			100.000

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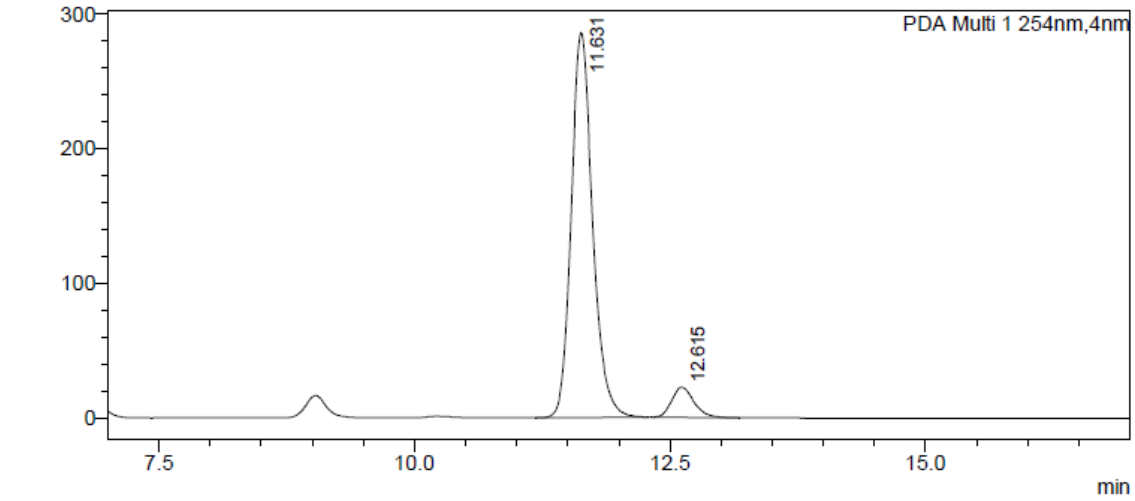
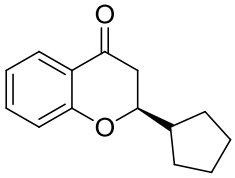


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	11.631	4158195	285571	0.000		92.412
2	12.615	341420	22514	0.000		7.588
Total		4499615	308085			100.000



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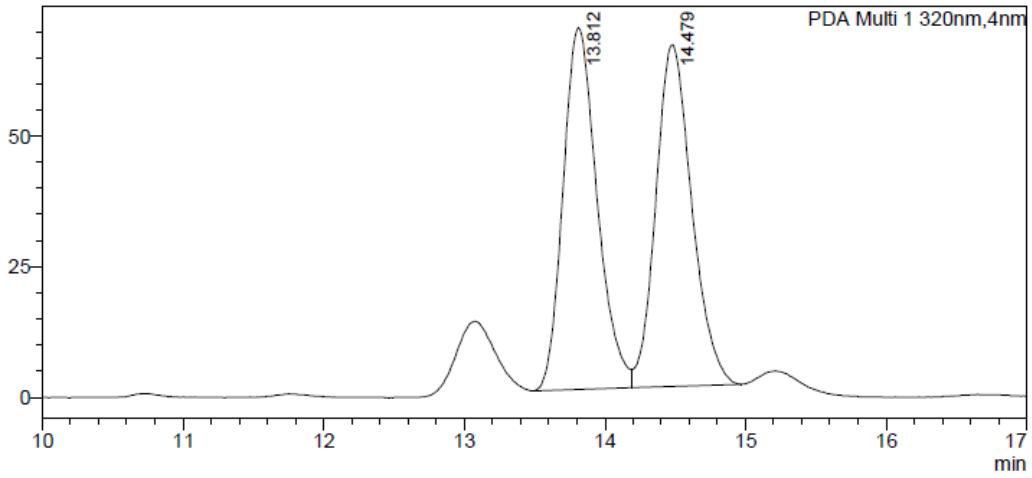
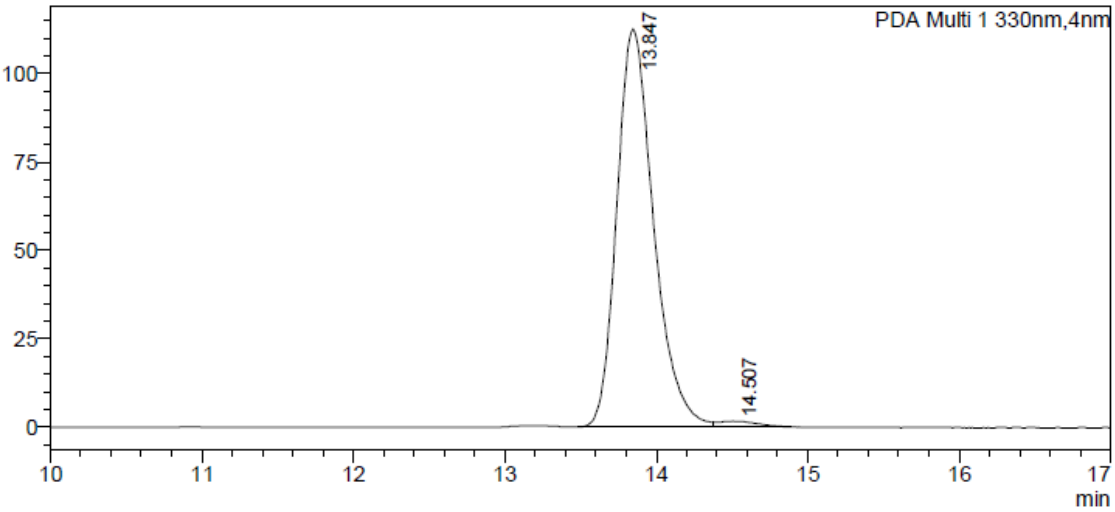


<Peak Table>

PDA Ch1 320nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.812	1167909	69298	0.000		50.059
2	14.479	1165158	65435	0.000		49.941
Total		2333067	134733			100.000

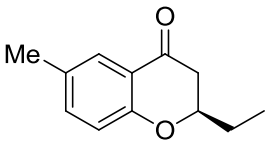
<Chromatogram>



<Peak Table>

PDA Ch1 330nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.847	1906764	112610	0.000		98.507
2	14.507	28892	1612	0.000		1.493
Total		1935655	114222			100.000



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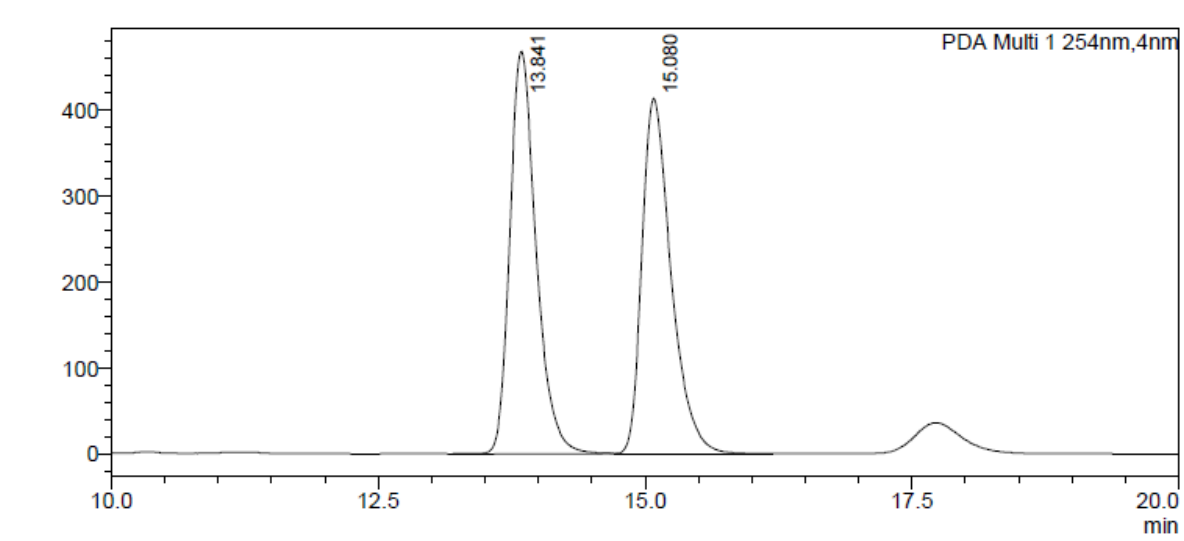

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.841	8029057	468059	0.000		50.475
2	15.080	7877882	413953	0.000		49.525
Total		15906939	882012			100.000

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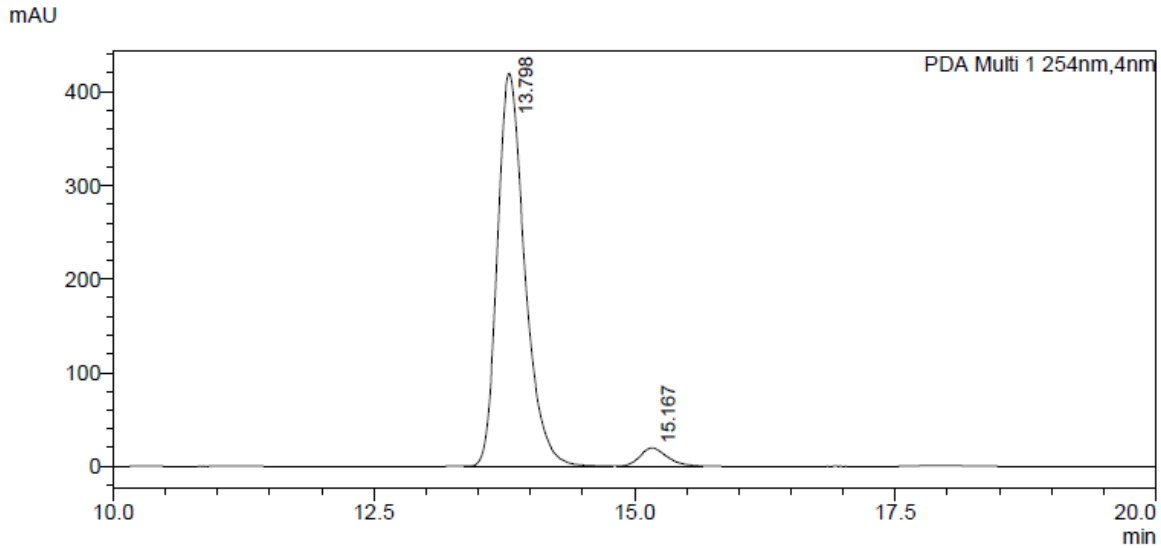
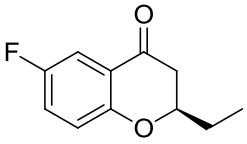


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.798	7643157	419178	0.000		95.670
2	15.167	345888	19122	0.000		4.330
Total		7989045	438299			100.000



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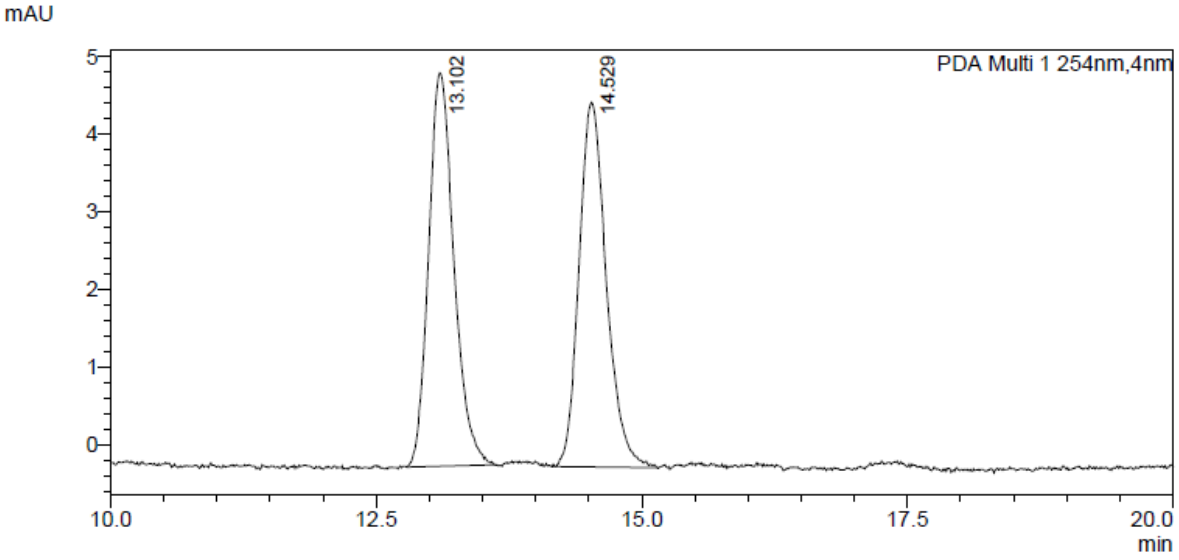
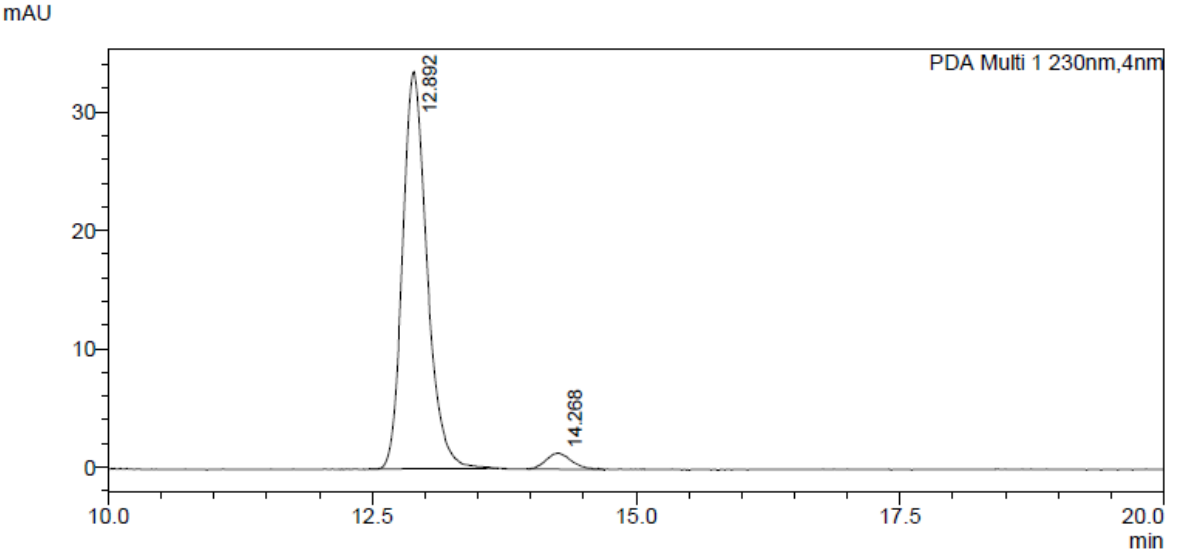


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.102	83865	5058	0.000		50.012
2	14.529	83823	4691	0.000		49.988
Total		167688	9749			100.000

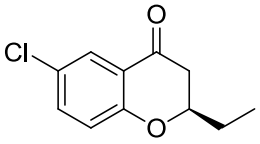
<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	12.892	540517	33549	0.000		96.000
2	14.268	22524	1348	0.000		4.000
Total		563041	34898			100.000



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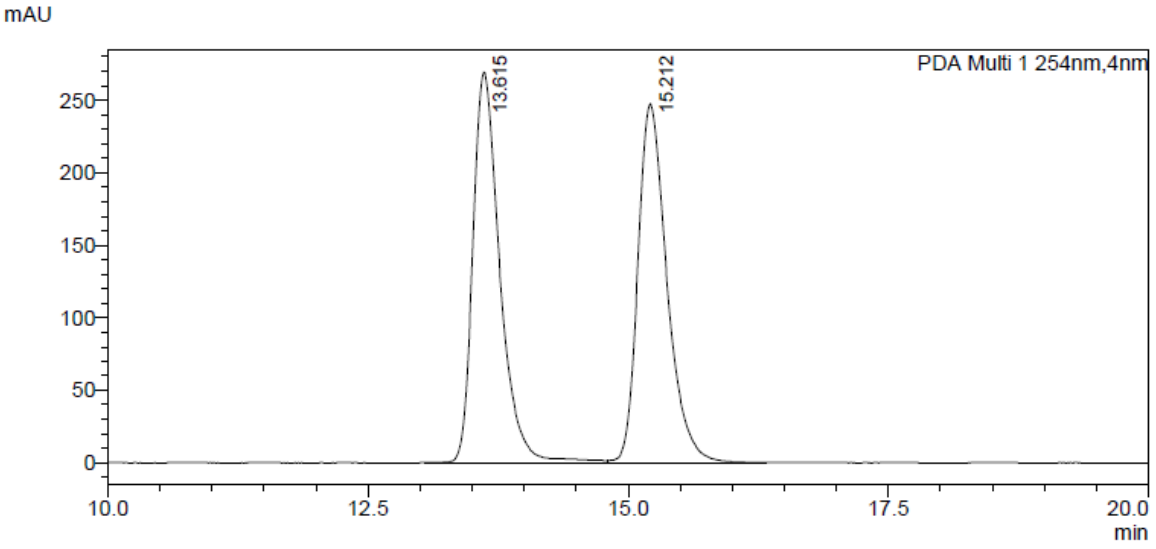

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.615	4863011	269364	0.000		50.266
2	15.212	4811590	247518	0.000		49.734
Total		9674601	516882			100.000

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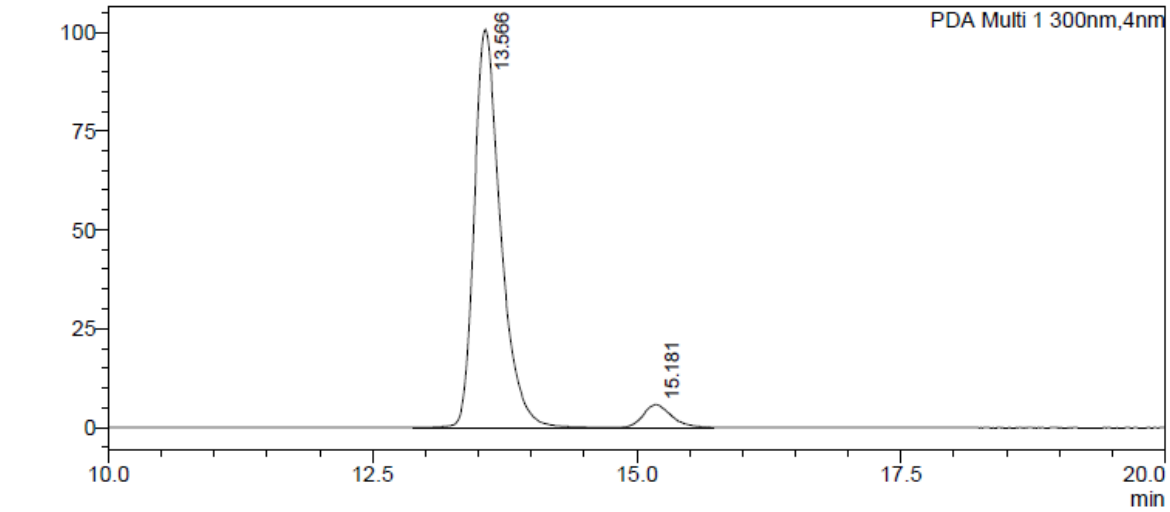
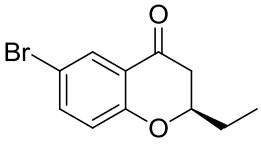


<Peak Table>

PDA Ch1 300nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	13.566	1746535	100575	0.000		94.356
2	15.181	104464	5691	0.000		5.644
Total		1850998	106266			100.000



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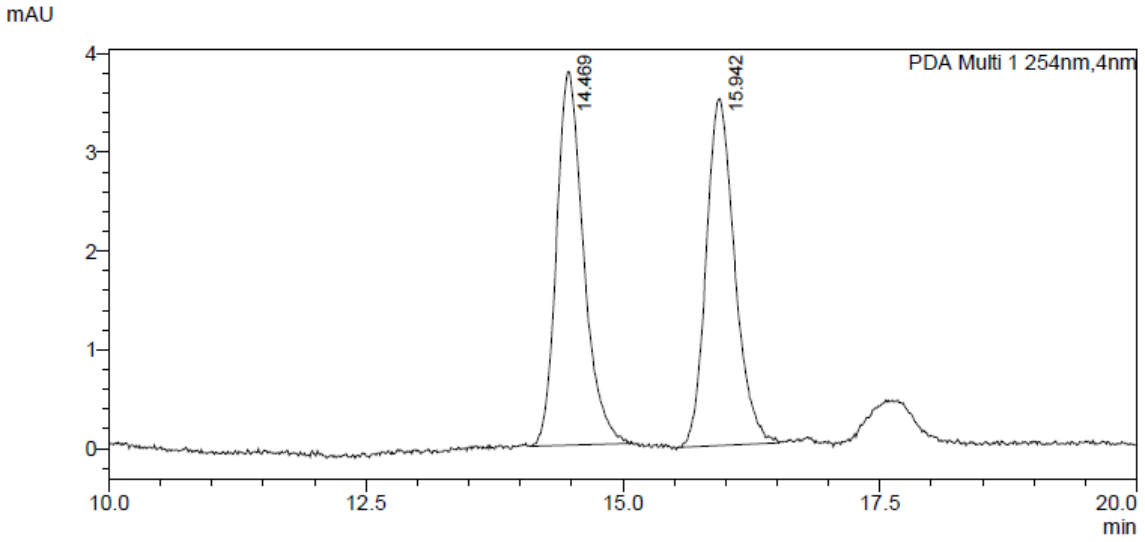

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	14.469	69399	3780	0.000		50.619
2	15.942	67701	3508	0.000		49.381
Total		137100	7288			100.000

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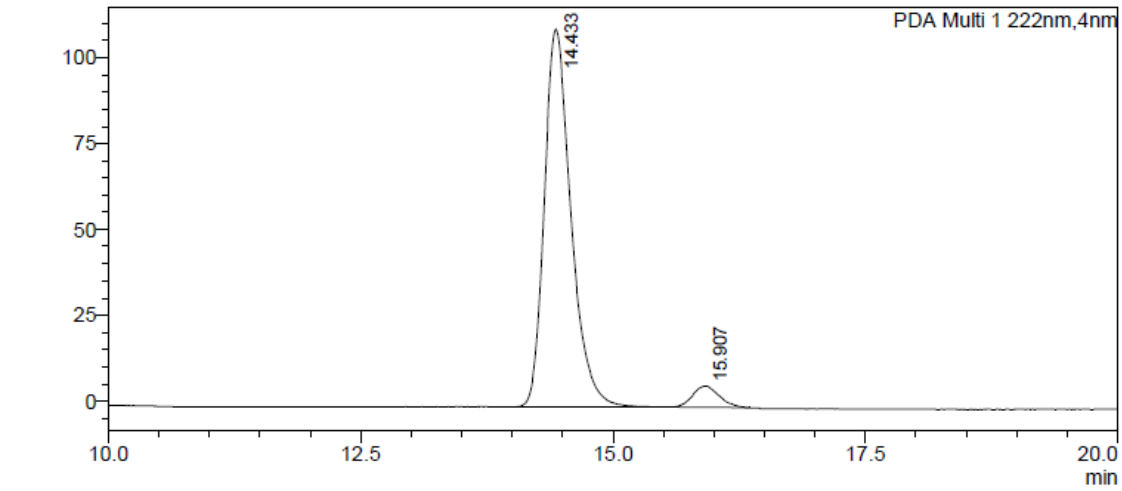
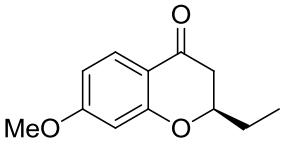


<Peak Table>

PDA Ch1 222nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	14.433	2020386	109906	0.000		94.656
2	15.907	114059	6212	0.000		5.344
Total		2134445	116118			100.000



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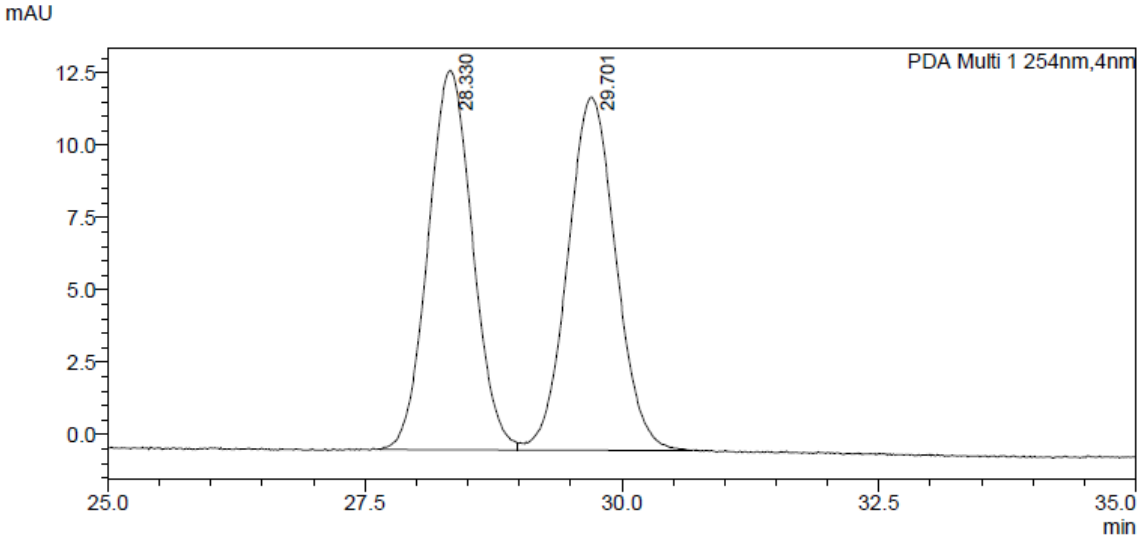
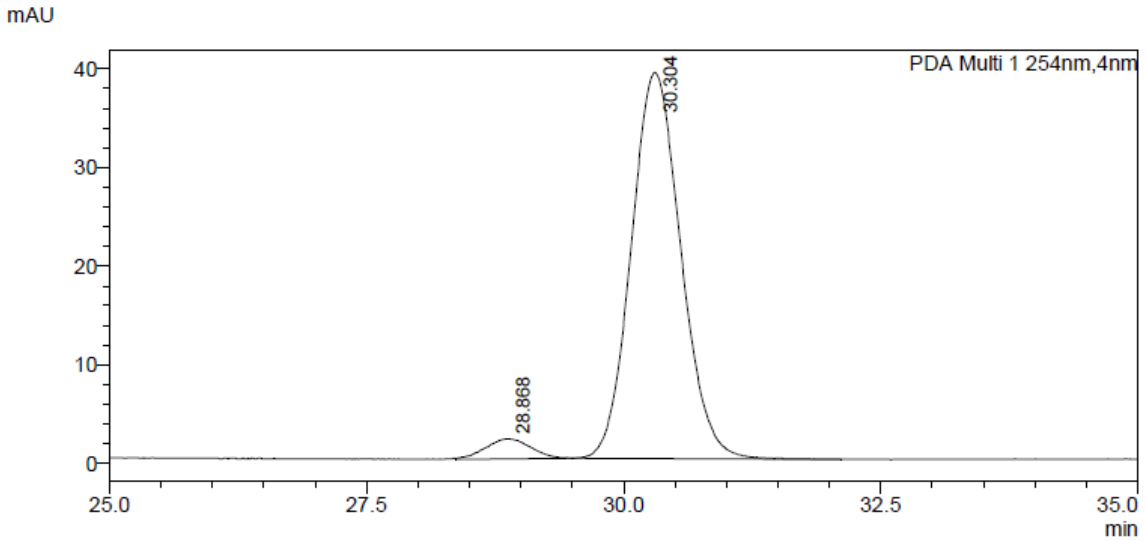


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	28.330	394173	13103	0.000		49.733
2	29.701	398405	12200	0.000		50.267
Total		792578	25303			100.000

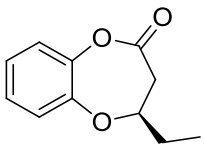
<Chromatogram>



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	28.868	62321	2037	0.000		4.534
2	30.304	1312316	39124	0.000		95.466
Total		1374637	41161			100.000



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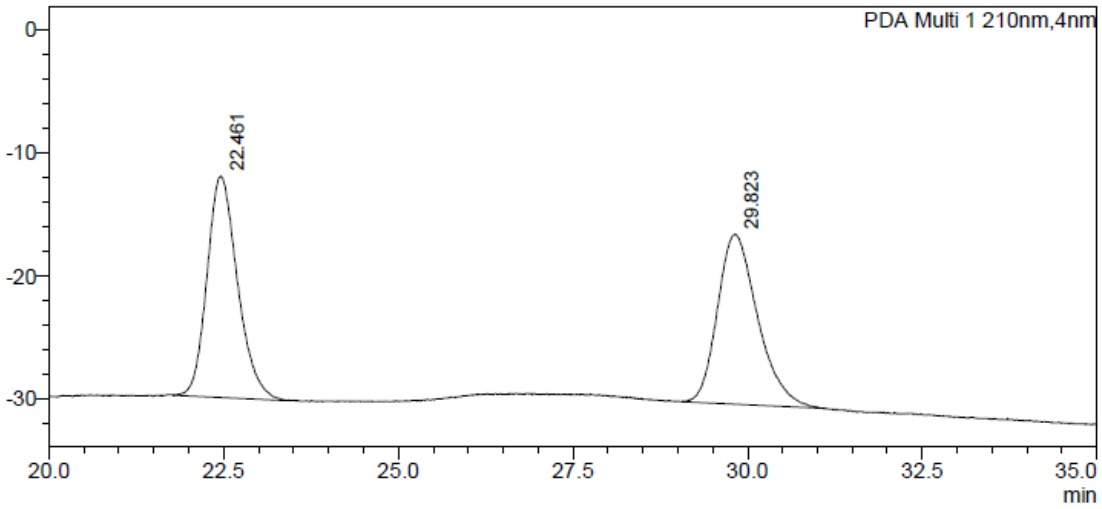

<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	22.461	544285	17975	0.000		49.772
2	29.823	549265	13777	0.000		50.228
Total		1093550	31753			100.000

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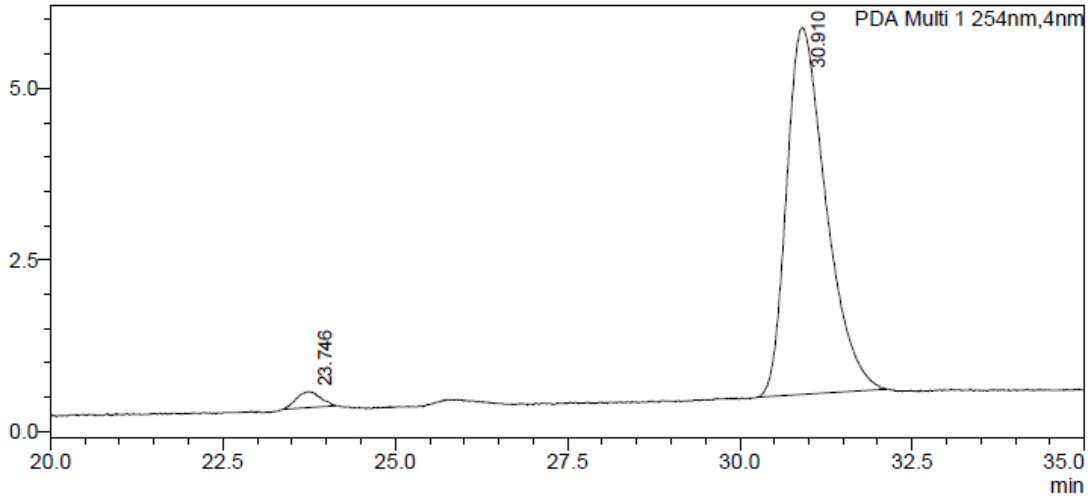

<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Area%
1	23.746	5667	234	0.000		2.599
2	30.910	212369	5338	0.000		97.401
Total		218036	5572			100.000